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MAN'S HEALTH AND THE ENVIRONMENT--SOME RESEARCH NEEDS

Task Force on Research Planning in
Environmental Health Science

March 1970

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MAN'S HEALTH AND THE ENVIRONMENT---SOME RESEARCH NEEDS

Report of the Task Force on Research
Planning in Environmental Health Science

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health
National Institute of Environmental Health Sciences

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TO: Dr. Paul Kotin
Director, National Institute of Environmental Health Sciences

We herewith transmit the final report of the Task Force on Research Planning in Environmental Health Science. This report places in your hands the carefully weighed and collective advice of more than fifty experts on urgent environmental health problems and possible means to their resolution. The recommendations range from highly specific to broad and general. In each instance, they arose from careful and responsible consideration.

We hope that this will provide a useful resource in the formidable task of developing a major national research effort to aid in resolving present environmental health problems and avoiding potential future difficulties.

It is important to emphasize that there are very important areas which were necessarily omitted from this report for reasons of time limitations. Their absence should not be taken as a judgment as to their importance or unimportance.

In passing this report on to you, we should like to call attention to some of those to whom tribute is due in this effort. A tireless and intellectually dedicated effort was put forward by all the Task Force members over the eighteen-month period of our work. Busy schedules required holding meetings on Saturdays to accomplish much of the preparatory work for the final three-week session; 100% attendance was the pattern. During the three-week period at Corvallis, work days were routinely sixteen hours in length.

Tribute is also due to those who so generously contributed to the work at Corvallis, not as official members of the Task Force but as representatives, in most cases, of Federal agencies.

The task of developing this report in the three-week period at Corvallis could not have been accomplished without the resources of Oregon State University, so generously made available to the Task Force. The Task Force is grateful to President Young, to our host Dr. Virgil Freed, and to his most able staff.

Special recognition is due the staff of the Task Force office at Corvallis. This operation was under the guidance of Dr. Valega of the NIEHS staff, ably assisted by Mr. McLaren of Dr. Freed's office. Also due special commendation were the skilled, indefatigable typists who were always abreast of the work placed upon them.

A large measure of gratitude is due Dr. Bernard Pasternack of the New York University, for his aid throughout this enterprise, and especially to Dr. Dade Moeller of the Harvard School of Public Health for his skill in the final editing of this report.

Finally, many thanks to you and your staff in NIEHS for the support and encouragement through the months of this effort.

We hope this document will aid you in your demanding assignment.

Norton Nelson

Norton Nelson
Chairman

James L. Whittenberger

James L. Whittenberger
Co-Chairman

Task Force on Research
Planning in Environmental
Health Science

March 10, 1970

Dr. Norton Nelson, Director
Institute of Environmental Medicine
New York University Medical Center
550 First Avenue
New York, New York 10016

Dear Dr. Nelson:

I was most gratified to receive from Dr. Kotin a copy of the Final Report of the Task Force on Research Planning in Environmental Health Science. That so many outstanding persons contributed so much time and energy to its preparation is a measure of both your organizing skill and the innate importance of the task.

The enthusiasm and confidence expressed during our conversations prior to the task force meeting have been more than justified, and it will be a privilege to point out to the Secretary of the Department of Health, Education, and Welfare the historic place that the report will occupy in our endeavor to ensure a healthful environment.

I am happy to report that some of the recommendations made by your task force have already been adopted by the National Institute of Environmental Health Sciences and that the topics have also been used as the basis of suggestions from the Environmental Health Service for research support by the Institute.

Please be assured that the impetus for research in the environmental health sciences provided by the report will be felt for a long time to come and that my office will continue to do all it can to see that the vision of the task force is rewarded with visible results.

I would like to take this opportunity to congratulate you and your associates as well as the task force members for a job well done with great dispatch.

Sincerely,

Robert Q. Marston, M.D.

Robert Q. Marston, M.D.
Director
National Institutes of Health

March 16, 1970

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MAN'S HEALTH AND THE ENVIRONMENT--SOME RESEARCH NEEDS

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MEMBERSHIP OF THE TASK FORCE

Dr. Norton Nelson, Chairman
Director, Institute of Environmental Medicine
New York University Medical Center

Dr. James L. Whittenberger, Co-Chairman
Director, Kresge Center for Environmental Health
School of Public Health
Harvard University

PROGRAM COMMITTEE

Dr. Hans L. Falk
Associate Director for Laboratory Research
National Institute of Environmental Health Sciences

Dr. James R. Fouts
Professor, Department of Pharmacology
Oakdale Toxicology Center
University of Iowa

Dr. Virgil H. Freed
Director, Environmental Health Sciences Center
Oregon State University

Dr. Sheldon K. Friedlander
Professor of Chemical Engineering and Environmental Health Engineering
Department of Environmental Engineering
California Institute of Technology

Dr. Leo Friedman, Director
Division of Toxicology
Bureau of Foods, Pesticides and Product Safety
Food and Drug Administration

Dr. Paul B. Hammond
Professor, Department of Veterinary Physiology and Pharmacology
College of Veterinary Medicine
University of Minnesota

Dr. James D. Hardy
Professor of Epidemiology (Environmental Physiology)
Department of Epidemiology and Public Health
Yale University

Dr. Ian T. T. Higgins
Chronic Disease, Adult Health and Aging Unit
Department of Community Health Services
School of Public Health
University of Michigan

Dr. Lawrence E. Hinkle, Jr.
Department of Medicine
New York Hospital—Cornell Medical Center

Dr. Harold C. Hodge
Chairman, Department of Pharmacology
School of Medicine and Dentistry
University of Rochester

MEMBERSHIP OF THE TASK FORCE

PROGRAM COMMITTEE (continued)

Dr. Paul Kotin
Director
National Institute of Environmental Health Sciences

Dr. Brian MacMahon
Head, Department of Epidemiology
School of Public Health
Harvard University

Dr. Robert C. Mellors
Professor of Pathology
New York Hospital for Special Surgery

Dr. David Minard
Professor and Chairman
Department of Occupational Health
University of Pittsburgh

Dr. Edward P. Radford
Professor, Department of Environmental Medicine
School of Hygiene and Public Health
Johns Hopkins University

Dr. Harold W. Wolf
Chief, Division of Criteria and Standards
Bureau of Water Hygiene
Environmental Health Service

MEMBERSHIP OF THE TASK FORCE

Subtask Force 1

Air Pollution

Dr. James L. Whittenberger, Chairman
Director, Kresge Center for Environmental Health
School of Public Health
Harvard University

Dr. Ian T. T. Higgins, Co-Chairman
Department of Community Health Services
School of Public Health
University of Michigan

Dr. Morton Corn
Professor of Occupational Health
Graduate School of Public Health
University of Pittsburgh

Dr. Benjamin G. Ferris, Jr.
Associate Professor of Environmental Health and Safety
School of Public Health
Harvard University

Dr. Bernard G. Greenberg
Professor of Biostatistics and Head
Department of Biostatistics
School of Public Health
University of North Carolina

Dr. E. Cuyler Hammond
Vice President, Epidemiology and Statistics
American Cancer Society

Dr. Sheldon D. Murphy
Associate Professor of Toxicology
School of Public Health
Harvard University

Dr. Jay A. Nadel
Associate Professor
Department of Medicine
Cardiovascular Research Institute
University of California Medical Center

Dr. William M. Thurlbeck
Professor of Pathology
Department of Pathology
McGill University

Dr. James Wei
Senior Scientist
Central Research Division
Mobil Research and Development Corporation

MEMBERSHIP OF THE TASK FORCE

Subtask Force 2

Community and Industrial Exposures

Dr. David Minard, Chairman
Chairman, Department of Occupational Health
University of Pittsburgh

Dr. Harold C. Hodge, Co-Chairman
Chairman, Department of Pharmacology
School of Medicine and Dentistry
University of Rochester

Dr. Arend Bouhuys
Professor of Medicine and Epidemiology
School of Medicine
Yale University

Dr. Edward R. Crossman
Professor of Industrial Engineering
Department of Industrial Engineering and Operations Research
University of California

Dr. Philip E. Enterline
Professor of Biostatistics
School of Public Health
University of Pittsburgh

Dr. Theodore Hatch
Professor of Industrial Health Engineering, Emeritus
Graduate School of Public Health
University of Pittsburgh

Dr. Morris A. Lipton
Professor of Psychiatry
Department of Psychiatry
Medical School
University of North Carolina

Dr. William H. Strain
Research Associate
Department of Radiology
School of Medicine and Dentistry
University of Rochester

MEMBERSHIP OF THE TASK FORCE

Subtask Force 3

Food and Water Toxicology

Dr. Leo Friedman, Chairman
Director, Division of Toxicology
Bureau of Foods, Pesticides and
Product Safety
Food and Drug Administration

Dr. Virgil H. Freed, Co-Chairman
Director, Environmental Health Sciences Center
Oregon State University

Dr. Harold W. Wolf, Co-Chairman
Chief, Division of Criteria and Standards
Bureau of Water Hygiene
Environmental Health Service

Dr. John C. Ayres
Chairman, Food Science Division
College of Agriculture
University of Georgia

Mr. Leonard B. Dworsky
Director, Water Resources and
Marine Sciences Center
Cornell University

Dr. Hans L. Falk
Associate Director for Laboratory
Research
National Institute of Environmental
Health Sciences

Dr. Leon Golberg
Research Professor of Pathology
Institute of Experimental Pathology
and Toxicology
Albany Medical College of Union
University

Dr. Joseph J. Harrington
Associate Professor of Environmental
Health Engineering
School of Public Health
Harvard University

Dr. Brian MacMahon, Head
Department of Epidemiology
School of Public Health
Harvard University

Dr. Herbert E. Stokinger
Chief, Laboratory of Toxicology
and Pathology
Bureau of Occupational Safety
and Health
Environmental Health Service

Dr. Gerald N. Wogan
Associate Professor of Food
Toxicology
Department of Nutrition and Food
Sciences
Massachusetts Institute of Technology

MEMBERSHIP OF THE TASK FORCE

Subtask Force 4

Physical Factors in the Environment

Dr. Edward P. Radford, Chairman
Professor, Department of Environmental Medicine
School of Hygiene and Public Health
Johns Hopkins University

Dr. James D. Hardy, Co-Chairman
Professor of Epidemiology
(Environmental Physiology)
Department of Epidemiology and Public Health
Yale University

Dr. George Bugliarello
Professor of Biotechnology and
Civil Engineering
Chairman, Biotechnology Program
Carnegie Mellon University

Dr. Alexander Cohen
Bureau of Occupational Safety
and Health
Environmental Health Service
U. S. Department of Health,
Education, and Welfare

Dr. William T. Ham, Jr.
Professor of Biophysics and
Head of Department
Department of Biophysics
Medical College of Virginia

Dr. Robert J. Hasterlik
Professor of Medicine
Department of Medicine
University of Chicago

Dr. Demitri B. Shimkin
Professor of Anthropology
and Geography
University of Illinois

MEMBERSHIP OF THE TASK FORCE

Subcommittee A

Epidemiology

Dr. Brian MacMahon, Chairman
Department of Epidemiology
School of Public Health
Harvard University

Dr. Ian T. T. Higgin, Co-Chairman
Department of Community Health Services
School of Public Health
University of Michigan

Dr. Arend Bouhuys
Professor of Medicine and Epidemiology
School of Medicine
Yale University

Dr. Morton Corn
Professor of Occupational Health
Graduate School of Public Health
University of Pittsburgh

Dr. Philip E. Enterline
Professor of Biostatistics
School of Public Health
University of Pittsburgh

Dr. Benjamin G. Ferris, Jr.
Associate Professor of Environmental Health and Safety
School of Public Health
Harvard University

Dr. Bernard G. Greenberg, Head
Department of Biostatistics
School of Public Health
University of North Carolina

Dr. Robert J. Hasterlik
Department of Medicine
University of Chicago

MEMBERSHIP OF THE TASK FORCE

Subcommittee B–1

Toxicology

Dr. James R. Fouts, Chairman
Professor and Director of the
Oakdale Toxicology Center
University of Iowa

Dr. Leon Golberg
Research Professor of Pathology
Institute of Experimental Pathology and Toxicology
Albany Medical College of Union University

Dr. Paul B. Hammond
Professor, Department of Veterinary Physiology and Pharmacology
College of Veterinary Medicine
University of Minnesota

Dr. Harold C. Hodge
Chairman, Department of Pharmacology
School of Medicine and Dentistry
University of Rochester

Dr. Morris A. Lipton
Professor of Psychiatry
Department of Psychiatry
Medical School
University of North Carolina

Dr. Sheldon D. Murphy
Associate Professor of Toxicology
School of Public Health
Harvard University

Dr. Herbert E. Stokinger
Chief, Laboratory of Toxicology and Pathology
Bureau of Occupational Safety and Health
Environmental Health Service

Dr. William H. Strain
Research Associate
Department of Radiology
School of Medicine and Dentistry
University of Rochester

MEMBERSHIP OF THE TASK FORCE

Subcommittee B–2

Toxicology

Dr. Hans L. Falk, Chairman
Associate Director for Laboratory Research
National Environmental Health Sciences Center
National Institute of Environmental Health Sciences

Dr. Leo Friedman, Director
Division of Toxicology
Bureau of Foods, Pesticides and Product Safety
Food and Drug Administration

Dr. Leon Golberg
Research Professor of Pathology
Institute of Experimental Pathology and Toxicology
Albany Medical College of Union University

Dr. E. Cuyler Hammond
Vice President, Epidemiology and Statistics
American Cancer Society

Dr. Edward P. Radford
Professor, Department of Environmental Medicine
School of Hygiene and Public Health
Johns Hopkins University

Dr. James G. Wilson
Department of Pediatrics and Anatomy
Children's Hospital Research Foundation

Dr. Gerald N. Wogan
Associate Professor of Food Toxicology
Department of Nutrition and Food Sciences
Massachusetts Institute of Technology

MEMBERSHIP OF THE TASK FORCE

Subcommittee C

Technological Trends

Dr. Sheldon K. Friedlander, Chairman
Professor of Chemical Engineering and
Environmental Health Engineering
Department of Environmental Engineering
California Institute of Technology

Dr. Harrison Brown
Professor of Geochemistry
Division of Geological Sciences
California Institute of Technology

Dr. George Bugliarello
Professor of Biotechnology and
Civil Engineering
Chairman, Biotechnology Program
Carnegie Mellon University

Mr. Leonard B. Dworsky
Director, Water Resources and
Marine Sciences Center
Cornell University

Dr. Joseph J. Harrington
Associate Professor of Environmental
Health Engineering
School of Public Health
Harvard University

Dr. Theodore Hatch
Professor of Industrial Health
Engineering, Emeritus
Graduate School of Public Health
University of Pittsburgh

Dr. James Wei
Senior Scientist
Central Research Division
Mobil Research and Development
Corporation

MEMBERSHIP OF THE TASK FORCE

Subcommittee D

Social and Behavioral Sciences

Dr. Lawrence E. Hinkle, Jr., Chairman
Department of Medicine
New York Hospital—Cornell Medical Center

Dr. Edward R. Crossman, Co-Chairman
Professor of Industrial Engineering
Department of Industrial Engineering and Operations Research
University of California

Dr. Alexander Cohen
Bureau of Occupational Safety and Health
Environmental Health Service

Mr. Leonard B. Dworsky
Director, Water Resources and Marine Sciences Center
Cornell University

Dr. Philip E. Enterline
Professor of Biostatistics
School of Public Health
University of Pittsburgh

Dr. Demitri B. Shimkin
Professor of Anthropology and Geography
University of Illinois

TASK FORCE SUPPORTING STAFF

Consultant:

Dr. Bernard S. Pasternack
Associate Professor
Institute of Environmental Medicine
New York University Medical Center

Executive Secretary:

Mr. Edward J. Lynch[1]
Program Analyst
National Institute of Environmental Health Sciences

Dr. Thomas M. Valega[2]
Health Scientist Administrator
National Institute of Environmental Health Sciences

Other Staff of the National Institute of Environmental Health Sciences:

Dr. Samuel S. Herman[3]
Associate Director for Extramural Research

Dr. Samuel Price[4]
Health Scientist Administrator

Miss Elizabeth Y. James
Public Information Specialist

Graduate Student Assistants, University of Oregon:

Don Babcock
James Baker
Ron Burr
Ray Cress
Robert Ellis
Robert Garnero
David Greiner
Michael Koeferl
John MacKenzie
Jonathan Schreiber
Charles Stanger
Jack Thorsen
Gerald Walsh

---

[1] Currently with the Office of Program Analysis, Office of the Director, NIH.

[2] Now a Physical Scientist Administrator with the National Institute of Arthritis and Metabolic Diseases.

[3] Currently Associate Director for Extramural Programs, National Eye Institute.

[4] Now a Health Scientist Administrator with the National Eye Institute.

PART I

INTRODUCTION

Charge to the Task Force
Foreword
Overview

CHARGE TO THE TASK FORCE ON RESEARCH PLANNING IN ENVIRONMENTAL HEALTH SCIENCE*

Paul Kotin, M.D.
Director, National Institute
of Environmental Health Sciences

The three-week meeting that begins today marks the fruition of an idea explored by staff and senior advisers of the National Institute of Environmental Health Sciences (then the Division of Environmental Health Sciences) during the winter of 1967–1968. Recognizing the need for guidance on research planning, we concluded that we could best meet this need by delegation, and the Environmental Health Sciences Advisory Committee (EHSAC) was requested to advise, and perhaps to assume sponsorship of a Task Force to develop such guidance. In March, 1968, EHSAC arrived at a decision to sponsor such a Task Force. The Council's subsequent recommendation for grant support of this effort set into motion a planning program notable for its thoroughness and the degree of involvement of the participants.

This is an appropriate moment to commend the approximately 50 leaders in environmental health research whose dedication over the past 18 months has made this occasion possible. Working sessions for the original executive committee, the program committee, the subtask forces, and the various subcommittees which frequently met during weekends and convened on short notice—were remarkable for the infrequent absenteeism of members. In all, there were over 20 meetings held at sites extending from coast to coast.

While there are a large number of goals built into the organization of the Task Force, they can, I believe, be conveniently divided into two major categories: (1) determine the status of current knowledge, primary problems, impediments to research progress, and objectives in selected areas of environmental health science; (2) identify key research needs and opportunities, as well as directions and strategies for future development.

The application and implementation of the achievements of this Task Force will, as you are aware, be dependent on resources, a subject loaded with imponderables at this time. One of the most important contributions this Task Force will make will be to provide the Institute with a solid scientific basis for working within the Federal structure to secure the necessary space, personnel and funds for carrying out its mission.

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* Presented to the Task Force at Corvallis, Oregon, on June 23, 1969.

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All of you are aware that research is the mission of the National Institute of Environmental Health Sciences. The common theme of deliberations during the next few weeks will be advancement of knowledge through research. The focus on research is implicit in the sponsorship and the priority assigned by NIEHS to this undertaking.

The triad of (1) needs for research, (2) priorities within needed research, and (3) strategies for the conduct of this research neatly shapes the arena of this Task Force effort and our Institute's activities.

Research is emphasized with full awareness that fundamental knowledge and its practical application are the end points of a spectrum of purposeful activity. There are no clear lines of separation in this continuous range of activity. Research cannot exist for long in a vacuum. The fact that you postulate a research need automatically implies that you see some deficiency in man's environment, some condition impairing his optimum health or efficiency, some situation that needs to be corrected. The acquisition of new knowledge and understanding provided by research is only a first step; a step which will remain unrewarded unless that new knowledge and understanding are transmuted into action. In consequence, your efforts, however fundamental their scope, cannot be considered independent of their significance and relevance to the problems of standard-setting, monitoring, regulation, and control.

This underscores the need for assurance that your deliberations will reflect the needs and concerns of practitioners, scientists, and administrators responsible for the application of knowledge accumulated through research.

It further accounts for the early involvement of staff from other Federal agencies in the Task Force preparations as well as the broad representation of environmental health interests that is apparent from the roster of participants. We have been very pleased with the way in which many individuals from what are usually regarded as action programs have joined your ranks in preparing this review of environmental problems. We have been very gratified with the interest shown by the policy-making members of the Consumer Protection and Environmental Health Service and other action programs, and we are delighted that their senior representatives join with ours in participating in and listening to the presentations of your deliberations. With us they will see the array of problems that you identify, the relative importances that you ascribe to them, and the suggestions from which we in NIEHS select specifics for intensive study. They will have the opportunity of knowing what we are thinking at the time we are first reviewing these problems, and of developing their own thoughts on how our potential studies will impinge on their programs of application and control. The liaison so strongly underscored at the birth of our organizations will find considerable fruition in the conduct of this conference.

The formal title of the Task Force—Task Force on Research Planning in Environmental Health Science—emphasized NIEHS as the prime beneficiary of these proceedings. It should be obvious, however, from the structure and agenda that the final report will be useful in varying degree to other organizations concerned with the problems of environmental health.

Recent experience has called attention to the frequently transient character of organizational arrangements. Examples of changes in organizational patterns are the Department of Health, Education, and Welfare reorganizations (Bureau of Disease Prevention and Environmental Control, Consumer Protection and Environmental Health Service, etc.), and the interagency transfer of responsibilities (U.S. Department of Interior and water pollution control). It is our hope that the Task Force's recommendations will have validity and applicability independent of present jursidictional boundaries, and I am firm in my conviction that its report will survive instabilities in our scholastic, governmental, and cultural practices. Organization in some areas is almost assuming a "du jour" character.

Since funds and other resources are never in sufficient supply, there is no escape from choices. NIEHS will not be able to implement in the near future all of the recommendations proposed by the Task Force. The Task Force's findings and recommendations will need to be translated into program formats that are consonant with fiscal constraints, congressional mandates, and other changing circumstances. The questions of mechanism of funding and appropriate administrative approaches must of necessity be determined secondarily by staff.

What we are seeking is a marriage of your sophisticated and learned advisory capabilities and mission with our executive branch responsibility so that the "issue" will effectively meet national need. The "moving boundary" nature of Federal action programs and responsibility reflects neither indecision nor feebleness of purpose, but rather the necessity to accommodate to such fluid considerations as wavering fiscal and other resources, management practices, and political and socio-economic considerations.

NIEHS hopes to derive from the Task Force's discussions a framework in which program choices can be made. Because of the magnitude and importance of the problems dealt with and because of the widespread interest in your deliberations, we plan to provide for unrestricted distribution of your report. The results of your efforts will provide an essential resource for our staff in the selection of particular program areas for special effort and expansion, while maintaining a wise balance among basic, applied, and resource efforts. It is obvious that a new task force cannot be called for every problem we face. For this reason, enduring reference to this Task Force Report and its associated recommendations as a framework within which to make the choices necessitated by *limited funds* can be practically assured.

In common with other units of the National Institutes of Health, NIEHS has the benefit of continuing and regular access to a broad array of public advisory groups, such as the Environmental Health Sciences Advisory Committee, Environmental Sciences Training Committee, and the Board of Scientific Counselors. In addition, NIEHS receives advice from an enlarging corps of individual consultants available on an *ad hoc* basis. With the help of these advisers, we pledge to apply our staff efforts at the highest level of skills to all stages of this joint activity from the Matrix you propose here to our Program—the mission-assigned responsibility which our staff gladly accepts.

FOREWORD

Dire predictions of the health dangers from environmental contamination are routine in the news media and are common topics of daily conversation. Some of the allegations are sound, others patently alarmist and exaggerated; for many, important data are lacking. In the last decade, it has become clear that the problems are too urgent to be blithely brushed aside and that ignorance must be replaced by information.

With population expansion and the growth of technology, the problems of environmental contamination have become increasingly apparent. Electric power generating capacity in the United States increased over 20-fold from 1920 to 1969. There are now some 45,000 registered pesticide formulations on the Federal rolls. Synthetic chemical production has more than doubled in the last ten years. These and other circumstances have led to intense national concern. Some evidence of the depth of this concern is illustrated by the variety of recent reports calling attention to environmental health problems; among them, the well-known Gross (1962), Tukey (1965), Spilhaus (1966) and Linton (1967) reports. This national concern has led to a major reorganization of Federal efforts in a variety of ways and has led, in particular, to the development in 1968 of an entirely new unit within the United States Department of Health, Education and Welfare, The National Institute of Environmental Health Sciences (NIEHS).

At the March 1968 meeting of the Advisory Council to the National Institute (then Division) of Environmental Health Sciences, Dr. Paul Kotin, Director of the unit, called for a discussion of approaches to ensure the maximum effectiveness of this new unit in fulfilling its urgent national mission. It was pointed out that, in contrast to many other government operations, this new organization represented an almost completely fresh start; that is to say, this program was being developed *de novo* and not through a reorganization of existing activities. In view of this special situation, Dr. Kotin asked the Council to provide a major set of planning guides to which he and his staff could have access in the development of the programs of the future Institute. After detailed discussion, the Council recommended that a group of people be asked to prepare a series of documented advisories on a research program which the Director could use, as he saw fit, in developing and allocating the resources available, or likely to become available, to the Institute. Thus, a Task Force on Research Planning in Environmental Health Science was launched as a function of the Advisory Council of the Institute.

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The Executive Committee of the Task Force, appointed by Dr. Kotin from the members of the Council, undertook the preliminary planning. This group, after having determined the general outlines of the approach, added members to constitute a Program Committee for the Task Force. This Program Committee was responsible for the planning and conduct of the operation which produced the report which follows.

The work of the Task Force was initiated during the spring of 1968 and continued through the ensuing year, culminating in a three-week intensive work session at Oregon State University, Corvallis, Oregon, from June 22 to July 12, 1969.

The general plan was to establish a Task Force of some 50 experts in the various fields of environmental health who would review in depth selected parts of this extremely broad field. On the basis of this review and their knowledge of current work, the members of the Task Force were asked to establish guidelines specifying the more important public health problems, designating those now amenable to resolution (and by what means) and suggesting how resources for solving the problems could be developed where it was considered that resources were not now available for successful attack.

As the work of the Task Force proceeded, it became apparent that it would be unrealistic to limit its planning effort solely to NIEHS research programs. Accordingly, the approach was taken of developing the recommendation without any prior commitment as to their appropriateness to NIEHS. For this reason, a number of the recommendations are not directed specifically to NIEHS and may be more suitable for other agencies. It is hoped that related agencies will study the proposals put forward in this report and find useful guidance in them. Among such agencies are the Consumer Protection and Environmental Health Service (now the Environmental Health Service) of the Department of Health, Education, and Welfare; the Federal Water Quality Administration of the Department of Interior; and other Federal Departments including Labor, Transportation, Housing and Urban Development, Commerce, Agriculture and Defense. Individuals from a number of these agencies participated in the preparation of the report. Representatives from all were invited to attend and comment during a discussion of an early draft and all suggestions received were taken into account in editing the final report.

The mission of the National Institute of Environmental Health Sciences was outlined during its organizational phases. The Institute is to concern itself with fundamental biomedical research on the health effects of a wide range of constituents in the environment of man. The NIEHS is particularly concerned with the deleterious effects on health resulting from long-term exposures to low-levels of chemical, physical, and biological substances, alone or in combination, in the environment.

The assigned mission is primarily related to the health effects of environmental agents upon man and is detached from immediate responsibility for the effect of man on the environment, interrelated as these may often be. The Institute is freed from the immediate burden of regulation and control, although it is held responsible for supplying the underlying knowledge required to make control possible, and regulation realistic and defensible.

The basic mission of the Institute is to provide backup information to various Federal agencies, uncluttered by categorical or administratively defined restrictions. This frees the Institute from any constraints associated with the administrative jurisdiction governing the particular medium in which the contaminant is found. Such freedom does not, however, relieve the NIEHS from the necessity of plotting a course which will be action oriented and thoroughly responsive to the developing needs of control agencies. Both of these roles are important and proper to the new Institute.

The Institute will have failed in a major sense, however, if it does not deliberately devote a substantial part of its effort toward better means of anticipating future difficulties. NIEHS must not become so immersed in catching up with today's problems that it permits the nation to be repeatedly vulnerable to unsuspected or unanticipated health threats. A policy which looks ahead to a predictive approach that can anticipate and avoid difficulty is imperative.

The research recommendations contained in the following chapters are directed not only to an intramural program which by 1976, it is anticipated, will engage a staff of some 1000 persons, but also to an extramural program which will, in time, fully utilize scientific resources in universities, research institutions and industry throughout the country. Indeed, it is anticipated that by far the larger effort will be found in the extramural program.

In planning the work of the Task Force, the approach was necessarily selective rather than comprehensive. The selectivity posed major difficulties and was based not on any confident prophetic sense of what is, or may become, important, but on the practical realization that the field of environmental health is far too broad to be adequately covered by any single effort such as the present one. This selectivity has led to omission or very light treatment of a number of areas of undoubted importance. This omission in no way implies the lack of importance of these fields or, indeed, of their relevance to the responsibilities of the Institute. In most instances, it reflects rather a practical recognition of the immensity of the task and the limited resources and time available to the Task Force. One major area which required omission for these reasons was the important one of traumatic injury.

The Task Force was subdivided along several different patterns. These are outlined in Appendix A. As may be noted, the entire Task Force was divided into four subtask forces with loosely defined boundaries and many areas of overlap. The same individuals, but in different configurations, also constituted four subcommittees which dealt with techniques common to different research areas. A fifth subcommittee concerned itself with the problem of predicting how technologic changes which may have health implications can be anticipated. Finally, a Program Committee, which consisted of the Chairman and Co-chairman of each of these groups, was also responsible for the examination of training needs and the organizational patterns for research.

Although the most intensive period of work was the three-week period in

Corvallis (during which the entire report which follows was written and rewritten many times), extensive preparation had already been completed before the Task Force assembled. This preparatory work took many forms but was mainly represented by the Background Documents which were prepared as resources for the Task Force deliberations. These Background Documents, some 45 in number, were written by individual experts to provide the working groups of the Task Force with a comprehensive review of various segments of the environmental health field. In each case, the objective was to summarize the present state of the art with specific comments on gaps in knowledge and needs in research. The Background Documents represent a valuable resource to any investigator or student who desires a thorough introduction to, and evaluation of, the many specific fields covered by these efforts. The titles and authors of these documents are given in Appendix B of this report; documents pertaining to specific topics are also listed at the end of appropriate chapters. The original manuscripts are in the repository of the National Library of Medicine. Copies may be secured on request to: National Library of Medicine, 8600 Rockville Pike, Bethesda, Maryland 20014.

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OVERVIEW

I. Introduction

Two convictions were held by a majority of the Task Force members: first, that the environment plays a predominant role in man's health; second, that rapid technologic change, increased population, and greater concentration of people into urban centers are compounding the problems of maintaining the environment at a healthful level. The agency within the Federal Government which has the responsibility for conducting, sponsoring, and fostering fundamental bio-medical research in these areas is the National Institute of Environmental Health Sciences. The Institute is particularly concerned with the deleterious effects resulting from long-term exposures to low levels of chemical, physical, and biological substances, alone or in combination. The purpose of this report is to provide guidelines to the Institute in carrying out this mission. It was prepared by a Task Force whose specific objectives were to determine the status of existing knowledge and to identify key research needs and opportunities, as well as directions and strategies for future development. Presented below are key problems cited by the Task Force in each of these areas and suggested recommendations for research.

II. Air Pollution (Chapter 1)

Deleterious health effects are well established for acute episodes of air pollution associated with specific meteorological conditions, for certain industrial exposures, and for cigarette smoking. It is impossible, however, to specify a level of air pollution that is safe for all elements of the community. Increasing the precision of the dose-response relations offers the only valid approach for establishing acceptable levels. Situations should be exploited which promise to illuminate specific questions.

The Task Force found that air sampling systems now in use are of limited value for measuring human exposure, and recommends that sampling characteristics be related to the nature of the biologic response. An important need in this regard is a "personal" sampling device which would give a quantitative measure of the concentration at the breathing zone as an individual performs his daily activities. Findings in normal healthy human subjects need to be compared with reactions of people with impaired physiologic function. Studies in children are also recommended because such studies avoid the complications of cigarette smoking and occupational respiratory hazards, and because children may be more sensitive than adults.

The Task Force supports the continuation of animal studies since these are essential for determining mechanisms of biologic response and for systematic studies of dose-response relationships.

III. Food and Water (Chapter 2)

Earlier successes in controlling food- and water-borne infectious diseases have led to a dangerous complacency. New information points out, on the one hand, the inadequacy of current microbiologic indices and the need for useful methods to detect specific pathogenic organisms and viruses, and, on the other, the need for better understanding of mechanisms of microbial pathogenicity, toxin production and the transmission of animal disease. Recent experience has emphasized the health significance of certain naturally occurring food components and underlined our ignorance of the non-nutrient components of ordinary foods. Little is known either from the laboratory or from epidemiologic studies of the possible role that our daily food plays in man's neoplastic and degenerative diseases. New foods, new processes, new methods of preservation, new packaging, new industrial chemical wastes, increasing use of fertilizers and pesticides and deteriorating water quality make increased research efforts imperative to assure the safety of food and water.

To meet this challenge, the Task Force recommends increased effort to improve analytical methodology for recognizing, characterizing and measuring microbiological and chemical agents in food and water; performance of supportive research to determine the mechanisms of the resulting biologic effects; and conduct of investigations to develop the required ameliorative measures, surveillance and control.

IV. Industrial Exposures and Consumer Products (Chapter 3)

Advances in technology are rapidly changing the industrial environment and in many instances creating new health problems. The Task Force recommends that a systematic investigation be made of occupational hazards based on measurements of the industrial environment and of the health of workers. A systematic sampling annually of 3,000 work places (of the 3 million in the United States) would permit the identification of those aspects of the environment relevant to health, provide a basis for inspection standards as well as for standards of environmental conditions, and permit definition of state and national goals for control of occupational hazards.

Workmen in industries where the risk of lung disease is suspected or known to be high should be regularly examined. Enzyme systems which will reveal the effects of exposures to toxic chemicals should be identified. The effects of exposures to atmospheric contaminants with concomitant stresses from physical factors, medications, altered physiological states, and intercurrent illnesses should be systematically explored.

As automation and mechanization increase, the occupational hazards from toxic exposures and machinery lessen, whereas those from decision-making and data-processing increase. Field studies of the short- and long-term health and efficiency of selected groups of industrial and service workers will help to gauge the importance of these factors. Paced decision-making, if it distorts the judgment of key persons (air traffic controllers, bus drivers), endangers the public safety. Safety limits should be established based on scientific tests. Perceptual and mental fatigue as well as performance decrements from environmental stresses (carbon monoxide, alcohol, noise, heat) need evaluating. The problems are clear; the techniques to provide answers require further development. Skill and experience in certain industrial accident studies emerge as preventive factors in reducing accident rates. This possibility should be explored and correlated with investigations of the role of improved product design in the acquisition of skill.

The evaluation of the toxic hazards of consumer products stands out as a pressing public health need. The first step—the identification of the categories of products involved in toxic injuries should immediately be attempted. The new hospital-based program of the Food and Drug Administration, developed jointly with the Environmental Health Service, is a promising beginning which should be developed on a national scale.

It is to be particularly noted that the number, diversity and increasing sophistication of composition of consumer products make more serious the current inadequacy of their evaluation for long term health efforts.

V. Physical Factors in the Environment, Including Living Space (Chapter 4)

Although there are new health problems arising, such as those from ionizing radiation, microwaves and lasers, the old problems of exposure to heat and cold, community noise, and crowded living space are still of major consequence. Stresses of the physical environment will increase with population growth, further urbanization, and greater energy use, and will place a desperate priority on attempts to build more suitable living space for urban groups.

The health effects of physical factors in the environment are pervasive, affect large populations, and may have major health consequences, including mutations and their effects on future generations. The Task Force noted, for example, that some community and non-industrial noise levels are beginning to reach intensities which have been associated with hearing defects in occupational groups. Similarly, it has been estimated that nearly one-half of the United States population lives in a measurable microwave environment. Concurrent with these conditions is a lack of data for setting acceptable standards for exposure. Microwave exposure standards for occupational exposure in the United States are set on the basis of thermal effects. Standards developed in the Soviet Union and other Eastern European countries, on the other hand, are based on nonthermal biological effects. Quite significant in the opinion of the Task Force, is the fact that the permissible level for microwave exposure in these countries is one thousandth the value accepted in the United States. With respect to humidity and infrared radiation, the United States does not even have a recommended standard.

The Task Force noted similar deficiencies in research on essentially all types of physical factors in the environment. One of the major problems is the marked dispersion of responsibility in this field at the Federal level. The Task Force strongly urges that primary responsibility for research in this area be assigned to a specific agency and that higher priority be given to research in all aspects of physical hazards in the environment.

VI. Epidemiology and Biometry (Chapter 5)

Deliberations of the Task Force confirmed that much more needs to be known about the implications to health of present and past exposures to environmental agents. Coupled with this problem is the fact that routine sources of data are inadequate for studying possible relationships between environmental exposures and disease or disability. Mortality statistics provide useful information in highly fatal diseases, but there is a need for information on a much broader scale than this. Morbidity statistics are even less satisfactory.

The Task Force called attention to the fact that epidemiologic study is applicable not only to disorders in which there may be a major, definable, etiologic agent, but it is also useful in evaluating disorders in which multiple environmental factors may interact among themselves and with personal characteristics of the host to produce disease. Especially important among this group are slowly developing manifestations such as cancer, cardiac and respiratory disease, and heritable disorders. In this connection, the Task Force pointed out that an "alert" mechanism to detect the presence of teratogens or mutagens in the environment can best be provided by surveillance of congenital malformations and heritable diseases and markers. To this end, there is a need for the establishment of a registry of congenital malformations in a defined population for use in surveillance and research into etiology. Concurrently, the reporting of hospital admissions should be made more comprehensive and existing cancer registries should be improved and fully exploited.

Apart from the conduct of epidemiologic studies, there are still major problems in their analysis. Further research is needed on methods of analysis of longitudinal data, on multivariate analysis and on epidemiologic models, including computer simulation. Demographic microsimulation models have been developed in recent years to study the effects of changing patterns in population growth. In this approach, the computer is used to generate from an initial population a complete vital history of each individual taking into account all the competing risks to which he is exposed. There are a number of problems in epidemiology where similar techniques would be beneficial.

VII. Epidemiologic Aspects of Carcinogenesis (Chapter 6)

Cancer is one of the major causes of death and as such is a public health problem of the first rank. Many environmental causes of cancer have now been identified, both from specific occupations and from cigarette smoking. Research has identified additional potent agents from natural sources. In addition, the possibilities are emerging that secondary factors ("promoting agents") may lead to frank malignancy where subthreshold levels of possibly ubiquitous carcinogenic agents are present. There is, in fact, a growing view that environmental factors may be responsibe for a great majority of all human cancers. For these reasons, the Task Force strongly recommends further study of occupational cancer, particularly cancer of the lung in uranium miners and asbestos workers and cancer of the bladder in workers exposed to chemicals. The Task Force also believes that the striking variation in cancer rates in different areas of the world provides a challenge and an opportunity to identify the environmental factors which must be responsible. International collaborative epidemiologic studies were cited as one possible approach to this problem.

If attention were to be focused on any one group of neoplasms of unknown cause, cancers of childhood, including childhood leukemia, probably deserve first priority. The incubation periods in these cases are clearly shorter than those of most tumors in adults. This should facilitate identification of the inducing agents. In addition, clinical associations between specific congenital malformations and certain childhood neoplasms suggest that some prenatal environmental factors may be common to both groups of diseases. The known greater susceptibility of rapidly growing tissue to carcinogens suggests on theoretical grounds that the child population should be watched particularly closely for evidence of the unintentional introduction of new environmental carcinogens.

VIII. Carcinogenesis, Mutagenesis, and Teratogenesis (Chapter 7)

Those concerned with safeguarding man's health must assure that the benefits of new technologies and new products are attained with minimal risk to man's health and well-being. To accomplish this goal requires new approaches. Rather than depending on hope, luck and hindsight (as has often been the case up to now), more careful surveillance of the health of the population and more systematized testing of the safety of individual chemicals now in use, or proposed for future use, must be employed.

Among the potential effects from chemicals released into the environment, three are of particular concern. These are carcinogenicity, mutagenicity, and teratogenicity. Contributing to the complexity of scientific investigations on these effects are the following shared features: their insidious nature; the relatively long time lag between exposure and overt effect; the irreversible nature of the resulting disease; the relatively great susceptibility of immature or developing tissue; the ability of etiologic factors, other than the one of interest, to produce the same endpoint; and the aggravation of effects from synergistic interactions. As a result, it is difficult to develop simple and reliable tests for evaluation of the products of new technologies and, in fact, new products are being introduced into our society faster than their safety can be ascertained.

An outgrowth of this situation is the fact that it is difficult to define or even estimate tolerance levels for the various chemicals being introduced into the environment. One approach is to declare "no tolerance" for potentially hazardous agents. If, on the other hand, a given level is to be permitted, one has to weigh carefully the risks of fatal, crippling or inheritable disease against the economic benefits of the proposed application.

To resolve these questions, the Task Force called for a focusing of research on those areas where existing activity is inadequate. Specific recommendations include a call for studies on the mechanisms of action of teratogens, comparative studies of the distribution, storage, and elimination of suspect chemicals, and the development of procedures for screening of all types of environmental agents for their pathologic effects. Lastly, the Task Force appealed to scientists to make negative and/or equivocal data on carcinogenesis, mutagenesis, and teratogenesis available in the published literature.

IX. Toxicology (Chapter 8)

In spite of the large investment of time and effort in research in toxicology, there are several areas that are relatively unstudied, particularly with respect to the needs of environmental health science. These include: (a) the problems of extrapolating results from animals to man; (b) the detection of early or relatively low levels of injury; and (c) approaches to the study of interactions of toxic agents to produce synergism or antagonism.

In the opinion of the Task Force, the overriding need is for improvement in animal testing procedures to increase the usefulness of animal data in predicting human responses. To this end, the Task Force recommended the instigation of extensive programs to broaden the knowledge of responses in many species and strains with the specific purposes of relating these responses to those in man. Since man is frequently exposed under conditions of stress, the Task Force urged that greater use be made of "stressed" animals in environmental health research.

In seeking more sensitive tests and the development of "early warning" systems, the Task Force suggested that behavioral or psychophysiologic tests in man exposed occupationally to noxious stimuli should be explored as a means for detecting effects before any of the classical chemical or physiologic tests become responsive. Recognizing that many clinically observed toxic interactions might have been prevented if existing pharmacologic information had been fully used, the Task Force also called for the computerizing of pharmacologic, physiochemical, and exposure (dose, duration) data as a means for developing a system for predicting adverse interactions of drugs and environmental toxic agents.

X. Social and Behavioral Sciences (Chapter 9)

Social and psychological processes help to create environmental hazards that contribute as much to morbidity and mortality as do many of the hazards that act through purely physical and chemical mechanisms. In addition, there are innumerable instances in which the technology is available for the prevention or elimination of environmental hazards, but it is not employed for personal, social or economic reasons. Recognition of the importance of these factors is exemplified by the fact that consideration of their implications may be found in nearly every chapter of the Task Force report.

In dealing with problems in this area, the Task Force believes it is important to recognize that (a) man's reactions to the people around him and to the social groups of which he is a member may have a major influence on any disease process; and (b) the effect of the environment on illness cannot be fully understood unless man is considered within the context of the social groups of which he is a part, and unless his perception of his environment is also considered.

To meet the urgent needs for research in this area, the Task Force recommends that the National Institute of Environmental Health Sciences organize a component for behavioral and social research. This component should include provision for an in-house capability to undertake important work such as the development of behavioral indicators of environmental insults, which might not be readily carried out on an extra-mural basis, and provision to plan and evaluate extra-mural work effectively.

In terms of specific research, the Task Force recommends that studies be conducted to define further the effects that man's perception of his environment has upon health, and the effects upon health that the environment itself produces through its influence upon the relations between people and social groups. It is also recommended that there be an expansion of research on the effects of the environment on the higher functions of the central nervous system, which are reflected in sometimes subtle changes in mood, thought, and behavior. In addition, research is needed on improving the instruments that are used to measure these effects.

XI. Technological Trends (Chapter 10)

There is a real danger that we may be fighting the last war rather than the one about to erupt. For this reason, there is an urgent need to develop on the national scene a continuing forecasting system which will undertake to anticipate over an appropriate time scale future changes in the structure of the technology and of the community relevant to human hazard. While certain aspects of the existing methodology of technologic forecasting are applicable to environmental problems, there is a need to develop a methodology specifically addressed to the environmental health field.

Most existing environmental health forecasting systems have been concerned with emission sources and levels rather than with problems of community exposure. Extension of these estimations to projections of community hazards requires models for predicting the transport, storage and reactions of pollutants in the environment. The past decade has seen a rapid development of mathematical models in these fields. The integration of these submodels into community hazard evaluation systems should be a major goal of environmental health forecasting programs.

The Task Force recommends that a significant portion of the forecasting capability should be directed to the coordination and inter-relation of control programs in traditional problem areas such as air, water and solid wastes. Too frequently in the past, the application of control procedures, such as process modifications, treatment processes, and legislative restrictions, have resulted merely in a shifting of the problem from one conventional category to another. The Task Force urges that the recommended forecasting capability anticipate such problems and incorporate techniques for their avoidance.

XII. Training (Chapter 11)

Talented, creative people, well trained and oriented toward the problems of environmental health, constitute the most important resource for implementing the kinds of research programs recommended by the Task Force. Unfortunately, past and present educational programs in this field encompass neither the number of individuals nor the scope of disciplines required to meet this need.

It is readily apparent that expanded and enriched programs are needed for educating and training greater numbers of scientists, administrators and specialists who possess diverse skills and outlooks and are familiar with the needs and problems in environmental health. In developing such a program, serious attention must be given to the problem of attracting capable students in a variety of disciplines to the environmental health area. The essential need is to make such students aware of the fact that few fields today offer comparably stimulating and complex intellectual challenges combined with such rewarding opportunities for service to mankind.

XIII. Organization of Federally Sponsored Environmental Health Research (Chapter 12)

The Subcommittee on Organization met after the recommendations on specific research proposals had been developed; accordingly it had at its disposal a sense of the dimensions and interrelationships arising from an integral involvement in these proposals as well as a sense of the magnitude and complexity of the task.

The primary goal of the National Institute of Environmental Health Sciences is to advance fundamental knowledge about the biomedical effects of environmental agents. To assure the attainment of this goal, the Task Force recommended that the Institute allocate a substantial portion of its resources to long-range studies and the development of efficient predictive techniques to aid in avoiding future health hazards. While the importance of certain short-term or *ad hoc* activities was recognized, in the opinion of the Task Force such activities should not be permitted to interfere with the Institute's basic long-term research mission.

In meeting its commitments with respect to the national environmental health research effort, the Institute should conduct and support the major part extramurally. Such an approach is almost mandatory in terms of the magnitude of the required research effort. It is also the only avenue by which the Institute can effectively utilize the larger national resource in science.

In special cases, research contracts can serve as an effective mechanism for the support of extramural activities. In general, however, the grant mechanism is more effective, particularly since it encourages the enlargement of the participation of academic institutions in environmental health research and research training. To facilitate this approach, the Task Force recommended that the number of university-based environmental health centers be expanded; that where the mission of such centers is broader than the mission of the Institute, consideration be given to their sponsorship by several Federal agencies on a cooperative basis; and that, wherever possible, new government laboratories be located in close proximity to major universities.

Other Task Force recommendations included the development of an explicit mechanism for the interchange of staff, both at the scientific and administrative levels, between the National Institute of Environmental Health sciences and other Federal agencies having responsibilities in environmental health; and the creation, under the Institute's leadership, of a formal mechanism for joint planning, evaluation, and coordination of environmental health sciences research projects at the Federal level.

PART II

RECOMMENDATIONS FOR RESEARCH ON SPECIFIC ENVIRONMENTAL PROBLEM AREAS

Chapter 1 Air Pollution
Chapter 2 Food and Water
Chapter 3 Industrial Exposures and Consumer Products
Chapter 4 Physical Factors in the Environment, Including Living Space

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Chapter 1

AIR POLLUTION

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AIR POLLUTION[*]

I. Introduction:

This Subtask Force was concerned primarily with the possible health effects of long-term, low-level exposure to the kinds of pollutants which characterize urban atmospheres. In dealing with the problem inherent in establishing dose-response relationships, the group also considered dose levels which occur in other sources of exposure—i.e., tobacco smoking; occupational dusts, gases and fumes; and specific community exposure problems associated with unusual meteorologic conditions or neighborhood pollution.

Death rates for pulmonary emphysema have been increasing steadily since about 1950 and chronic nonspecific pulmonary disease has become a leading cause of disability in adult males. Air pollution has been suggested as one of the possible explanations which must be seriously considered.

The etiologic role of air pollution in other major diseases has also been a matter of concern. Two of these—lung cancer and heart disease—have been strongly associated with cigarette smoking, but community air pollution could also be considered a contributory factor. Epidemiologic studies are ambiguous in regard to such a role for air pollution in lung cancer; suggestive evidence also exists with respect to heart disease, since physiologically significant amounts of carbon monoxide are present in cigarette smoke and in many community atmospheres. It remains to be determined whether carbon monoxide has a significant role in the incidence or course of heart disease.

Another type of concern about air pollution results from the presence of specific chemicals known to produce disease in occupational exposures. Examples are compounds of lead and asbestos. The great usefulness of these compounds suggests the possibility of their continued presence, if not increase, in the environment and, accordingly, their potential for harm must be carefully examined.

Looking at the study of air pollution effects as a problem in toxicology, it is quickly recognized that the levels of specific pollutants and mixtures of pollutants in community atmospheres are well below the range which the toxicologist usually examines with the standard techniques available. When he attempts to duplicate long-term exposures at "realistic" levels, he encounters so many complicating variables that the interpretation of a long-term animal experiment

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[*] The Subtask Force which developed this Chapter was chaired by Dr. James L. Whittenberger and co-chaired by Dr. Ian T. T. Higgins. Individuals who contributed to the information presented included Drs. Morton Corn, Benjamin G. Ferris, Jr., Bernard C. Greenberg, E. Cuyler Hammond, Sheldon D. Murphy, Jay A. Nadel, William M. Thurlbeck, and James Wei.

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is just as difficult as the analysis of comparable "natural" experiments with human populations. Nevertheless, there is much worthwhile information to be gained from animal experiments. Characterization of biological effects, mechanisms of action, synergistic effects of combinations of pollutants and other stresses, and certain behavioral effects are examples of studies that can most profitably be done with laboratory animals.

The task of gaining specific knowledge of health effects through human studies is notably difficult. The effects of some pollutants can be studied in planned human exposures, and this should be done, but there are serious ethical and medico-legal problems to be dealt with, and furthermore the interpretation of physiologic or biochemical responses to acute exposures is very limited in terms of induction of disease.

The problems besetting the environmental epidemiologist are no less imposing. Matching exposure data with observed health effects which may take many years to develop is an exceedingly difficult task, since there is so little reliable information about air pollution both over time and in space, since the health effects are typically influenced by several factors, and since true exposure histories of individuals are non-existent.

These problems and proposed research to solve them are dealt with in the sections which follow.

II. Need for Epidemiologic Studies

Present evidence is inadequate to specify safe levels of pollution. Further effort is therefore needed to increase the precision of dose-response relationships. These relationships need to be established not only for the population as a whole but also for those segments of the population which may be most vulnerable, such as the young, the old and those with chronic respiratory, cardiac and other diseases. This is the only way that standards which are based on scientific evidence rather than opinions or guesses can be set. This topic has been extensively reviewed, particularly for oxides of sulfur and particulates (Anderson, 1967; Goldsmith, 1968; Heimann, 1967; NAPCA, 1969a and 1969b).

Theoretically, dose-response relationships should be available for individual pollutants and also for various combinations. It is doubtful if this ideal can be attained in an epidemiologic setting. The best that is likely to be practicable is to exploit situations in which one kind of pollutant predominates. There is at least one city known (Rotterdam, the Netherlands) where concentrations of sulphur oxides in the air are high but particulates are low; others should be sought.

Clarification may also be provided on the importance of interactions of pollutants by studies in countries, such as Britain, where the implementation of legislation has resulted in an appreciable reduction of smoke but no change in the level of sulphur oxides. In the United States, too, the effect of any reduction in pollution which may result from the institution of air quality standards should be measured not only to assess the need for these standards but also to gain additional information on permissible levels.

III. Problems of Exposure Measurement

True measurement of exposure has not been made in any epidemiologic study of long-term effects. A variety of indices have been used, in the hope that they would be valid at least for comparative purposes. These include descriptive variables such as urban vs. rural, visibility interference, and characterization of areal pollution through measurements of one or more gaseous or particulate pollutants.

Some general attempts have been made to characterize the atmosphere in the form of national or regional networks in which a number of pollutants have been measured on either a continuous or intermittent sampling basis. Most of these studies involve a single sampling station per city and give a limited picture of the extent and kinds of pollution in American cities. Most components have not been in existence long enough to give trends. The resulting data are not of epidemiologic use since no systematic account of population density or character of the biologic response was included in the sampling design.

A. Sampling Design

Even with improvements in sampling design, analytic methods, and integration of exposure in space and time, it is improbable that the ideal of a complete exposure history of any sample of people over a long period of time can ever be attained; in all probability, the use of the crude approximations implicit in occupational exposure history, residential history, current and life time smoking histories, etc., will have to be continued. Improvements would be of value, however, in providing better information about spatial distribution, indoor-outdoor differences, and personal exposure. Improved techniques would also be more efficient in meeting the needs for monitoring.

1. Tissue Measurements

Additional methods of characterizing exposures to pollutants need to be developed. Some estimate of dosage for those pollutants which are retained in the body can be made by measuring the concentration of the pollutant in the tissues. Lead, beryllium and asbestos are examples of pollutants which can be assessed in this way. In order to form an accurate opinion on the dosage which has been received, adequate knowledge about the metabolism of the pollutant in question is essential.

2. Personal Sampling

A second and potentially more versatile approach is the use of a device similar to a radiation dosimeter. A personal sampling device might be developed to integrate exposure in the breathing zone over a considerable period of time and movement through space. This information could then be correlated with that obtained from sensors at fixed locations established according to grid patterns to make the latter information more useful.

B. Sampling Frequency

The nature of the biologic response to pollutants and the time relationships of uptake, reaction, and inactivation or elimination, are important determinants of the requirements for the timing and frequency of sampling (Roach, 1966). The plan of sampling for sulfur dioxide (SO_2) would obviously need to be different than that for carbon monoxide (CO). The reaction of SO_2 is largely reflex and very prompt, in a matter of seconds to minutes; a briefly sustained peak of concentration would cause a reaction, whereas there would be no measurable response if the same total exposure were spread over a 24-hour period. With CO, there is a time requirement measured in hours before an equilibrium concentration is reached which has a predictable physiologic effect. Excretion is also slow. The sampling plan for CO can therefore ignore transients for the more meaningful 8-hour and 24-hour averages. In fact, the slow response time for CO makes the body a good integrator of CO exposure. As a result, a blood level of CO is an accurate indicator of biologic stress.

C. *Needs for Improvement*

Improvements are needed in several aspects of air sampling and analysis as now practiced. Acquisition of the large amounts of data required would be greatly facilitated if there were simpler and less expensive methods for analysis of the common pollutants. Present methods are costly in terms of total input (materials, labor, apparatus) and are often nonspecific.

There is also a need for comparison of fixed sampling points versus mobile units from the standpoint of validity and reliability. Mobile sampling is currently used in some European countries to obtain exposure data for judging the response of vegetation to pollution.

D. *Data Summarization*

After large volumes of data regarding exposure are accumulated, the question arises as to how the data should be described or summarized in order to relate them to response. In many situations, it will suffice to examine an average and various measures of variability. The average and variation, however, may not be adequately descriptive of the hazards involved for certain pollutants. For pollutants individually or in combinations, the following other possible factors should also be considered:

1. Cumulative exposure over a given time period.
2. The number and intensity of extremes in a given time period.
3. The proportion of a given time period during which any specific level has been exceeded.

In relating the measure of dose to response, there is the statistical problem of knowing how to take into account low levels of exposure over long periods of time. Moreover, how early in life would it be feasible to start using a personal sampler? There will also be problems involving the tracing of individuals over long periods of time. There are two approaches to this; one is the retrospective history of the individual and the other is the prospective history. Each of these creates different statistical methodological problems and more study should be devoted to them.

E. Data Interpretation

Finally, because there will be many pollutants and multiple types of response, there are other statistical aspects needing attention. These include the:

1. Use of multivariate techniques in analysis of data.
2. Use of Bayes estimation in studying the size and distribution of parameters.

F. Recommendations:

On the basis of the above considerations, the Subtask Force makes the following recommendations for research in solving the problems of exposure measurement:

> **_Recommendation 1–1:_ Studies should be initiated to determine the usefulness of personal air pollutant samplers to measure the exposure dose to representative individuals.**
>
> **_Recommendation 1–2:_ Efforts should be made to extend existing studies to determine the characteristic biologic response times which affect the requirements for sampling duration, frequency, and averaging times for different pollutants.**
>
> **_Recommendation 1–3:_ The development of modeling techniques for air basins should be extended. The objective should be to predict concentrations of pollutants at ground level and at elevations, taking into account that such techniques should be consistent with the biologic response pattern of human beings for the pollutant in question.**
>
> **_Recommendation 1–4:_ The Subtask Force encourages the development of simpler and less expensive methods for sampling and analyzing suspended particulate matter, sulfur dioxide, nitrogen dioxide, carbon monoxide, and other pollutants.**
>
> **_Recommendation 1–5:_ Studies should be initiated to determine the feasibility and reliability of a random sampling scheme based on use of a mobile sampling unit. These studies should include the necessary macro- and micro- meteorologic investigations.**
>
> **_Recommendation 1–6:_ Studies to assess the relevance of existing National Air Sampling Network and Continuous Air Monitoring Program network information to the different aims of air quality monitoring and measurement of human exposure should be extended. Again, this will necessitate supporting meteorologic studies.**
>
> **_Recommendation 1–7:_ The Subtask Force encourages the development and improvement of statistical methodology for dealing with the problems of dose-response relationships over long periods of time.**

IV. Indices of the Effects of Air Pollution

There are a number of indices which can be used for measuring the effects of air pollution. Two common indices are mortality and morbidity.

A. Mortality

Mortality, though possibly a rather insensitive measure of biological effect of low pollution levels, still provides useful information. Mortality for all causes and for certain specific causes such as respiratory diseases, and cancer of the lung and other sites, should be used whenever possible. Analysis should be by age and sex for specific groups (Hechter and Goldsmith, 1961; Martin, 1964; Winkelstein, *et al.*, 1968).

B. Morbidity

Morbidity includes absence from school, work, or usual activity which can be attributed with reasonable confidence to illness, admission to hospital, emergency visits to clinics, insurance sickness claims, etc. As in the case of mortality, morbidity for all causes and for specific causes may be used and the observations should, whenever possible, be presented by age-sex specific groups. The importance of improving indices of morbidity in studies of environmental agents is discussed at greater length in the chapter on Epidemiology and Biometry (Chapter 5).

In studies in which the data are collected by individual investigators, more precise measures of incipient and frank morbidity may be used (Waller and Lawther, 1955; Spicer, *et al.*, 1962). Respiratory and other symptoms may be carefully recorded using standardized questions, as, for example, those recommended in the British Medical Research Council's respiratory symptoms questionnaire. In assessing the effect of air pollution on symptoms, it is essential that other factors which may also cause the symptoms should also be carefully noted. This implies that adequate smoking and occupational histories should be included (Fairbairn and Reid, 1958; Olsen and Gilson, 1960). To obtain an accurate estimate of a person's lifetime dosage of pollution, a full residential history is needed.

C. Method Standardization

Objective measurements are important and standardized methods, which have been extensively tested and widely used in the past and found reliable, should be continued in present and future studies. This will ensure comparability among different observers and with past findings. Those measurements which have proven most useful have been tests of respiratory function, in particular of ventilatory capacity. Recently additional tests of lung function have become practicable in field surveys and these may increase the sensitivity with which the effects of low levels of pollution may be measured. Examples of the more recent tests which have proved useful include the measurement of respiratory resistance, the diffusing capacity or transfer factor for carbon monoxide, and volume-flow spirometer tracings. In addition to the assessment of respiratory function, tests applied to the other systems, especially the cardio-vascular, central nervous sytem and special sense organs, need to be investigated.

D. Recommendations

The Subtask Force offers the following recommendation with respect to the indices of the effects of air pollution.

Recommendation 1–8: **Further epidemiologic studies are needed to establish more precisely the relationship between pollutant concentrations and mortality, morbidity, physiologic and psychologic impairment. Such studies should be carried out in representative samples of the general population, in suitable occupational groups and in persons who are thought to be particularly susceptible to pollution: Examples include:**

a. Correlation of daily mortality and morbidity with daily variation in meteorologic factors and changes of air pollution levels in large cities.

b. Correlation of daily variation in respiratory well-being with daily variation in air pollution in patients with chronic respiratory disease. The use of daily diaries and more objective methods of assessment, for example, by regular simple lung function tests, should be considered in such studies. A wider range of more detailed lung function tests might be applied to long-stay patients in hospitals.

c. Correlation of mortality, morbidity, symptoms and physiologic function with levels of air pollution in persons who live in places which differ in pollution. Examples include differences in pollution within cities, between cities and between urban and rural areas.

d. Longitudinal observations of suitable groups to measure any changes in mortality, morbidity, symptoms and physiological function, which might be attributable to any changes in air pollution which may result from current legislation.

e. Studies in children, which appear likely to be particularly useful for assessing the effects of pollution on morbidity, symptoms and lung function. Further studies of children attending schools, which differ in their amount of pollution, should be pursued. Consideration should also be given to the possibility of following a sample of children, born into areas which differ in pollution levels, from birth to adolescence, to determine differences in incidence of illnesses which might be attributable to pollution.

f. Further studies of migrants, of monozygotic and dizygotic twins, of fertility, foetal development and foetal loss in relation to air pollution.

g. Studies to improve the accuracy of diagnosis in epidemiologic studies. These are particularly needed in the area of chronic respiratory diseases and specifically in the more accurate differentiation of chronic bronchitis and emphysema. Every attempt should be made to secure competently performed examination of the lung in autopsies on those who have been studied in such surveys.

h. Studies designed to determine the value of newer tests of pulmonary function now available for survey use.

i. Epidemiologic studies of occupational groups to establish variations in the incidence of cancer of various sites. Such studies should not be limited to workers exposed directly to the pollutants but should also include persons living in the vicinity of the factory who are moderately exposed and represent a gradation in dose. By selecting different occupations with varying pollutants, the probability is enhanced for studying synergistic effects and the influence of multiple causes.

j. Studies aimed at identifying specific causative agents in cigarette smoke. Identification of the specific ingredients of cigarette smoke that are responsible for the association between smoking and ill-health remains an important problem. In particular, steps should be taken to determine whether low tar and nicotine cigarettes are less hazardous than others. The possibility that

combinations of agents rather than single components are responsible must be kept in mind. These matters must be investigated not only in relation to carcinogenesis, but also with respect to the many other deleterious effects of cigarette smoke on the respiratory and cardiovascular systems.

k. Further studies to determine whether cigarette smoking has a synergistic action with other compounds in the production of cancer or other disease states. Such action has been suggested between cigarette smoking and uranium mining in the development of lung cancer.

V. Studies in Experimental Animals

Toxicologic research oriented to community air pollution has dealt primarily with sulfur and nitrogen oxides, ozone and other oxidants, carbon monoxide, simple mixtures of these chemicals with aerosols or other gases and vapors, and with complex mixtures of only partially characterized consitution. Except for studies on the carcinogenic potential of air contaminants, little attention has been given to investigation of organic air pollutants, even though it is established that organic acids, aldehydes and ketones are emitted in appreciable quantities from various combustion sources (or formed by chemical reactions in the atmosphere), and some of these (e.g., acrolein, formaldehyde) are strong irritants.

A. Purposes of Research with Animals

The purposes of specific studies on the effects of air contaminants on laboratory animals have been: (a) to test hypotheses that contaminants may be causally related to a known human disease, (b) to characterize the biologic effects, (c) to determine dose-response relationships in order to estimate the maximum levels which will be non-injurious to man, and (d) to determine the biologic mechanisms of the response. The first three goals often have immediate applications. The practical implications of mechanism studies are less apparent, but they may be most important to an understanding of the effects of mixtures of contaminants, to identification of contaminant-biological reactions which lead to disease and to the development of more sensitive indices for detection of effects and rational means of therapy or control procedures.

Previous toxicologic studies on community air pollutants have focused largely on effects in the lungs and airways. This is logical since many air contaminants are irritants of mucous membranes and are likely to produce injury at their first site of contact with sensitive tissues. There is some evidence, however, that extra-pulmonary effects may result from exposure to air contaminants which have in the past been considered as primarily irritant in their actions. In experimental animals these effects have been manifested as changes in behavior (Boche and Quilligan, 1960; Murphy, 1964), reproductive function (Kotin and Thomas, 1957; Lewis, *et al.*, 1967), endocrine function (Fairchild and Graham, 1963) and blood and tissue enzymes (Murphy, 1965). Of course, many air contaminants, e.g., CO, metals, solvent vapors, have primarily systemic actions. It is important, therefore, that studies of the effects of air pollutants should emphasize the use of a variety of indices of response. It is also important that studies be performed in such a way that the time-and-dose-response relationships for different types of effects can be evaluated.

B. Recommendations

Consideration of the research requirements in these several areas forms the basis of the following recommendations.

> ***Recommendation 1–9:*** **Much more study is needed on common air pollutants to determine mechanisms of response and relationships between reactions to acute and to prolonged exposure. Such information would improve the basis for air quality criteria development.**
>
> ***Recommendation 1–10:*** **Increased attention should be given to the newer emission products associated with developments in industrial, military and aerospace operations. (See Chapter 10)**
>
> ***Recommendation 1–11:*** **Increased emphasis should be placed on studies of the combined actions of gaseous and particulate pollutants.**
>
> ***Recommendation 1–12:*** **Attention should also be given to the possible synergistic effects of other environmental components and of modifying factors in the organism itself. Examples would be meteorologic variables (temperature, fog) and factors in the organism such as exercise, disease or allergic states, adaptation, and presence of other foreign chemicals or drugs.**
>
> ***Recommendation 1–13:*** **Effort should be directed toward the development or selection of animal disease models which resemble air pollution-sensitive individuals or groups in the human population.**
>
> ***Recommendation 1–14:*** **Comparative studies of the physiology, biochemistry, and morphology of the lung should be encouraged in order to provide a logical basis for a) understanding the mechanisms of environmental influence, and b) comparing results in animals and man. Additional fundamental work is especially needed on pulmonary clearance mechanisms; the production of surfactants; release, uptake, and metabolism of endogenous pharmacologically active compounds; and immunologic reactions.**

VI. Laboratory Studies of Human Beings

Biologic differences between species make it desirable to obtain information directly from human beings.

A. Acceptable Studies

Experimental exposures must avoid undue risk to the subjects but, with proper safeguards, studies in the following areas may be justified:

1. Exposures of industrial workers to contaminants present in the industrial environment (for example, cotton and other dusts).
2. Exposures to substances in concentrations known to exist in the atmos-

phere. Higher concentrations could be used if shown not to have serious or irreversible effects in animals.

B. Human Studies in the Past

Past studies in the laboratory of the effects of air pollutants have been performed in different ways:

1. Exposure of individuals via masks or in environmental chambers where the concentration of the pollutant is monitored continuously.
2. Exposure of individuals to the ambient (polluted) air followed by a period in which the air is filtered. This type of study has generally been less informative than the first, but has been considered preferable when the subjects include people with serious pulmonary disease. (Motley, *et al.*, 1959).

C. Research Considerations

1. Acute Exposures

Most laboratory experiments with human beings involve short exposures (frequently only a few minutes). The advantage of acute exposures are: a) the experiment can be better controlled, b) risks are minimal, and c) dose-response relationships are easier to establish. On the other hand, acute exposures give only limited insight into changes which may occur. For example, acute exposure to 5 parts per million of sulphur dioxide may increase the airway resistance; with longer exposure adaptation of the nerve fibers may occur and the resistance may return to the control level.

2. Species Differences

In addition to differences between species, differences within members of the human species must also be considered. Inhaled irritants which have a mild bronchoconstrictive effect in normal subjects may cause severe bronchoconstriction in some asthmatic subjects and in some other patients with chronic obstructive airway diseases. Thus, it is important to study those individuals with obstructive lung disease who have the greatest risk of serious deterioration in lung function following exposure to air pollutants. Furthermore, no satisfactory animal model of some human respiratory diseases (e.g., asthma) exists, so relevant studies can be performed only in patients.

3. Possible Synergistic Effects

Most of the studies in human beings have been limited to the effects of single pollutants. It is also important to study the possible interactions of atmospheric contaminants under controlled conditions. Irritant gases such as sulfur dioxide cause bronchoconstriction in experimental animals and in human beings. Aerosols which are otherwise inert may potentiate the effects of some irritant gases in producing bronchoconstriction in guinea pigs (Amdur and Underhill, 1968). This evidence has been used to explain how low concentrations of irritant gases in air pollution episodes lead to serious deleterious effects on respiratory function. However, these effects have never been demonstrated in human subjects.

Another example of possible synergism is the interaction of carbon monoxide and other contaminants on cellular function. Because of its capacity to interfere with oxygen transport to the tissues and thus to affect cardiovascular and central nervous system function, carbon monoxide has a broad capacity to potentiate biological responses. Since significant levels of carbon monoxide are inhaled by cigarette smokers, it is critically important to evaluate further its effects, particularly on the central nervous and cardiovascular systems, in healthy individuals and especially in patients with diseases of the blood or cardiorespiratory systems.

4. Microstructures

The microstructures which comprise the pulmonary system have received a great deal of attention in recent years. Such components as mucous cell, mucus, ciliary function, surfactant, and alveolar cell types including alveolar macrophages have been under investigation.

Very few studies involving the uptake and release of pharmacologic substances in the lung have been conducted on human beings, although there is much information from animal experiments indicating that the lungs are actively producing, detoxifying, storing and taking up substances which are pharmacologically active in the body.

D. Recommendations:

Recommendation 1–15: More studies are needed to quantify the responses of the human respiratory, cardiovascular, and central nervous systems to acute and chronic exposures to single pollutants and to combinations of pollutants in association with various climatic factors. This should include normal and "sensitive" subjects under appropriate safeguards. The effects of stresses such as exercise should also be studied in the above conditions where feasible.

Recommendation 1–16: There is a need for more studies to correlate clinical symptoms and tests of pulmonary function performed during life with findings at autopsy. These efforts should include study of the _in vitro_ mechanical properties of the lung, with the purpose of providing a better understanding of the ways that inhaled agents may be related to development of pulmonary disease, aging processes, susceptibility to infection, and allergic manifestations.

Recommendation 1–17: Autopsies resulting from accidental death should be studied in relation to previous exposures. Information on smoking habits, occupation, areas of residence and previous illnesses should be obtained from the next of kin. The reliability of information from the next of kin should be assessed when possible by comparing it with information obtained from the decedent before death.

VII. Summary

Health effects of air pollution are well-established for acute episodes of increased illnesses or deaths associated with specific meteorological conditions, for certain industrial exposures, and for cigarette smoking. Less definite is the evidence for association of long-term low level exposures with the incidence of chronic diseases such as emphysema, heart disease, and lung cancer. There is also concern with possible health effects of specific chemicals such as lead, asbestos, and beryllium in community atmospheres.

Recommendations for research are outlined in this chapter under the broad categories of community studies (assessment of exposure and measurement of effects), laboratory studies involving experimental animals, and laboratory studies involving man. In reviewing the subject, the Subtask Force was selective rather than comprehensive, giving scant attention to some aspects of the field, for example, aeroallergens. This in no way implies unimportance or lack of relevance of the problems omitted. In the paragraphs which follow, several generalized comments are made concerning the specific recommendations given earlier in this chapter.

A. Community Studies

With respect to community studies, the Subtask Force has given separate attention to the problems of estimating exposure and the problems of assessing biologic responses of the populations exposed.

1. Measurement of Exposure

There are problems of sampling and problems of analysis, data processing, and prediction. The requirements for monitoring and for estimating human exposure are very different; none of the sampling systems now in use provides the data needed for measuring human exposure. Modeling techniques for air basins may be of help in improving predictions of pollutant concentrations as they vary in space and with time (Recommendation 1–3). Costs in labor and equipment are serious impediments to the collection of the kinds and amounts of data needed, even for the common pollutants. To alleviate this situation, the Subtask Force encourages the development of simpler and less expensive methods for sampling and analysis (Recommendation 1–4). It is also suggested that the possible advantages of a mobile sampling unit over a fixed grid system be explored (Recommendation 1–5). As a part of this evaluation, there is a need to extend the studies for assessing the relevance of the information being obtained through the existing fixed grid systems (Recommendation 1–6).

A major factor in the validity of sampling technique is recognition of the importance of relating sampling characteristics to the nature and timing of biologic response (Recommendation 1–2). Very little information of this kind is available. Another important need is a "personal" sampling device which would give a quantitative measure of the concentration at the breathing zone as the individual carried out his daily activities (Recommendation 1–1). Finally there are problems of developing statistical methods which are appropriate for handling these kinds of data (Recommendation 1–7).

2. *Indices for Human Response.*

Mortality, morbidity, and impairment of various physiologic functions have been used as indices for human response; all such measurements must take into account concurrent exposures to cigarette smoke and occupational respiratory hazards. Studies in children are especially recommended because these complicating variables are avoided and children may be more sensitive to air pollution than adults. These and other types of epidemiologic studies are recommended to improve the precision of the dose-response relationship for various combinations of pollutants (Recommendation 1–8).

B. Studies in Experimental Animals

Attempts to simulate human population exposures in chronic animal studies have not been very successful, but animal experimentation is essential for determining mechanisms of biologic response and for systematic studies of dose-response relationships with various combinations of gases, gas-aerosol mixtures, and added stresses both external and internal. The Subtask Force calls for increased research on problems in each of these areas (Recommendations 1–9, 1–11, and 1–12). Greater emphasis should also be given to the newer emission products associated with developments in industrial, military and aerospace operations (Recommendation 1–10).

Animal disease models should be developed further for the testing of air pollutants on the more susceptible elements of a population (Recommendation 1–13). As with other aspects of toxicology, much more fundamental work is needed on comparative physiology, biochemistry, pharmacology, and immunology of the lungs to improve understanding of responses to environmental insults and to improve predictability of similar responses in man. Animal studies are also essential to further elucidation of clearance mechanisms of the lungs (Recommendation 1–14).

C. Laboratory Studies Involving Man

The final step in extrapolating animal data to human responses is to test man under controlled and safe conditions. Criteria development and standard setting almost demand that this be done. Some important findings in experimental animals have not proved valid for man. More studies are needed for quantifying human responses to acute and chronic exposures to single pollutants and to combinations of pollutants in association with various climatic factors. Findings in normal healthy subjects need to be compared with reactions of people with impaired pulmonary function. The effects of stresses such as excercise on these responses should also be studied where feasible (Recommendation 1–15).

Behavioral tests for reactions to pollutants such as carbon monoxide are especially appropriate in man. There is much to be learned about correlations between functional and clinical data on the lungs and the post-mortem morphology of the lungs (Recommendation 1–16). In addition, autopsies resulting from accidental deaths should be studied in relation to previous exposures (Recommendation 1–17). Finally, tests of systems other than respiration should be developed, eventually to be used in epidemiologic studies.

BACKGROUND DOCUMENTS

Document Number	*Author*	*Title*
AP–1	Higgins, I. T. T.	Epidemiological Studies of the Effect of Air Pollution.
AP–2	Murphy, S. D.	Use of Laboratory Animals to Assess the Effects of Air Pollution on Human Health.
AP–3	Corn, M.	Measurement of Human Exposure to Air Pollution in the Community.
AP–4A	Ferris, B. J.	Tests to Assess Effects of Air Pollutants on Human Health.
AP–4B	Nadel, J. A.	Technics for Measurement of Effects on Humans in Laboratory Experiments.
AP–4C	Greenberg, B. G.	Measurement of Effects upon Humans: Statistical and Epidemiological Aspects.
AP–5	Hammond, E. C.	A Hypothesis on Cancer Etiology and Pathogenesis.

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Chapter 2

FOOD AND WATER

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FOOD AND WATER*

I. Introduction

Animal life is dependent on the environment for the basic essentials of air (oxygen), water and food. The ability to sustain life in the absence of oxygen is measured in minutes, in the absence of water in days and in the absence of food in weeks. Although maintenance of an adequate supply of the essential nutrients and their presentation to the organism in a proper balance is an essential aspect of the relation of food and water to health, the primary concern of the Subtask Force was with the non-nutrient aspects of food and water. Two basic questions were involved: (a) What are these non-nutrient components, and how much of each is present? (b) What are their biological effects and what is the health significance of these effects in terms of the concentration found in the environment?

From the standpoint of infectious diseases, it is the living components in food and water that are of primary importance. The response to these components generally occurs in a relatively short time after exposure, producing acute effects. Non-living components in food and water sometimes cause acute injury and at other times may cause subtle or chronic effects that are so long delayed from time of exposure that the correlation of cause and effect is very difficult. Similarly, the relationship of environmental causes to man's many metabolic and degenerative diseases is obscure and difficult to demonstrate.

From the standpoint of overall research priorities in the field of environmental health, the greatest need is to develop methods for the evaluation of the long term effects of environmental agents. One of the basic requisites to meeting this need is the development of adequate indices to detect the presence and significance of such agents. In this regard, it is pertinent to note that the water, foodstuffs, and food processing procedures that are accepted today without reservation as to safety and wholesomeness enjoy this acceptance entirely on the basis of short term observations.

With respect to food and water, consideration must be given to substances that are present in relatively large amounts (that is, parts per hundred), as well as to those that are truly minor components (that is, present in terms of parts per billion). The criteria of purity, obviously, must be considered not from the

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* The Subtask Force which developed this chapter was chaired by Dr. Leo Friedman, assisted by Co-Chairmen, Dr. Virgil H. Freed and Dr. Harold W. Wolf. Individuals who contributed to the writing of the chapter included Drs. John C. Ayres, Leonard B. Dworsky, Hans Falk, Leon Golberg, Joseph J. Harrington, Brian MacMahon, Herbert Stokinger, and Gerald N. Wogan.

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point of view of "how pure?", but "is it pure enough?" Questions such as these should be answered by toxicological criteria rather than by analytical criteria.

Also to be considered is the fact that a variety of substances released into the environment prove to be very mobile and tend to translocate to areas distant from their point of origin. Transport by wind, water and other agents, has resulted in global distribution of such substances as chlorinated hydrocarbons and radionuclides. The dynamics of escape, transport and partitioning of substances into living organisms is an area of increasing interest and significance for environmental health.

The initial sections of this chapter relate to research recommendations concerning the use of water in potable form for drinking and food preparation. Considered in other sections are applications of water for domestic, municipal, industrial, agricultural, and recreational uses, and for the cultivation and harvesting of aquatic and marine life. These uses present potential health hazards due to biological and chemical contaminants which must be evaluated and controlled. Problems in this area are increased by the growing pressure to reuse water both for potable and non-food purposes.

II. Microbiology of Food and Potable Water

Food scientists are concerned about the continuing prevalence of gastro-enteritis and gastro-enteritis-like illnesses. In recent years there has been an increasing gap between the rate of technological changes in certain segments of the food industries and the level of effort being made to evaluate and control the hazards associated with new products and processes. Radical departures from conventional procedures in production, processing, preservation, packaging, distribution and utilization of foods have raised questions concerning microbiological contamination of products in partially or completely prepared form now reaching large segments of the public. Increased attention needs to be directed toward developing the knowledge and techniques necessary to evolve a more wide-reaching and vigorous national program to coordinate efforts of industries and government so that the consumer receives adequate protection.

Most conventional water treatment systems have been designed primarily for the control of bacterial pathogens. Historically, these systems have been eminently successful. Control is based largely on chlorination, the effectiveness of which is dependent upon the quality of the water. The deteriorating quality of water sources throughout the nation, a lag in the Federal support of developmental research on new water treatment systems, and the inability or unwillingness of municipalities and industry to finance the necessary development, are together resulting in narrowing of the margins of safety. These deficiencies have increased apprehension among public health and water works officials.

This environmental decay can in a large measure be attributed to the nation's technological growth. Despite this growth, the environmental health control programs at the federal level have been dwindling and suffering through a number of major reorganizations (three in less than four years). Research needs are becoming more urgent every year.

In examining the problems that have been enumerated in the area of food and water microbiology, it became apparent to the Subtask Force that these problems can be categorized into the following three broad areas: Methodology, Mechanisms, and Evaluation of Technology.

A. Methodology

Methodology is concerned with the detection, identification and evaluation of microorganisms and viral agents in food and water. Studies in this area are relevant both for purposes of monitoring and for developing new techniques appropriately fitted to specific media.

Recommendation 2–1: **Rapid, reliable, and adequate techniques for the isolation, identification and quantification of the viruses and pathogenic bacteria in foods and water need to be developed.**

The most important water-borne pathogenic virus, that of infectious hepatitis, still cannot be cultivated. Gastroenteritis outbreaks of unknown etiology but suspected to be of water-borne viral origin continue to be exported (Green, *et al.*, 1968). Viral contamination of foods occurs, generally, via the water route. Investigations of viruses in food and water are hindered by the low concentrations of these infectious agents. New concentration procedures, recently developed, need additional study (Berg, 1967; Oliver, 1967; Dack, 1963).

A diversity of tests are available for detecting and identifying pathogens such as Salmonellae, staphylococci, Shigellae, Clostridia, etc., and pseudomonads in foods and water; yet these tests are neither rapid nor reliable. For example, the conventional tests used to detect *Salmonella* in foods require at least four or five days to reach the stage where the organisms can be identified with any degree of certainty. No single screening procedure will give all *Salmonella* of importance, yet this organism was involved in the most recent large scale water-borne outbreaks. The ubiquity of *Salmonella* makes this organism a top priority target for public health workers (Summers, 1969). Insofar as staphylococci are concerned, authorities differ regarding the use of solid—as opposed to liquid—media (Prost and Riemann, 1967; Casman, 1965).

Recommendation 2–2: **Procedures for isolation and enumeration of a) pseudomonads and b) fecal streptococci in food and water need to be developed. Such studies should include the development of standardized media, particularly for culturing enteric bacteria.**

Pseudomonads have presented unusual difficulties in storage of water in plastic containers, aftergrowth in faucet strainers, and proliferation in filtration equipment and carbon adsorption treatment systems. Since these organisms may also cause infections among swimmers, their public health significance needs study. Procedures and media presently in use do not delineate these potential pathogens from many of the ordinary psychrophilic flora found in food and water.

Streptococci can be valuable tools for evaluating the sanitary quality of water. The use of these organisms has been limited largely because of conflicting results concerning media and methodology (Geldreich, 1969; Kabler, 1962).

Investigators in various laboratories have experienced great difficulties in repeating work of others even though both sets of workers use the same medium. Different batch-lots of these media often give variable results. Similarly, media from two different commercial manufacturers often give widely different results. Since sanitary indices for potable water and food are based on measurements using such media, this is an area of direct public health concern (North and Bartram, 1953).

***Recommendation 2–3:* Studies are needed to determine the reliability of indicators and/or indices as these relate to a) the coliform index and the presence or absence of viruses in foods and water, b) fecal coliform indicators as a substitute for total coliforms, c) the coliform indicator concept and the control of pathogenic bacteria, and d) the total bacterial count and its application to potable water quality (particularly as it relates to renovated water).**

Coliform organisms have been used as indicators of sanitary quality for water for decades, yet it has long been known that their absence does not assure absence of viral or bacterial pathogens. For example, the traditional coliform index failed to forewarn of two important water-borne epidemics by *Salmonella* and *Shigella*, i.e., the Riverside and Madera episodes. For this and other reasons, it is desirable to find alternative or new indicators of pathogenicity (Kabler, *et al.*, 1964; Fair and Geyer, 1954; Greenberg and Ongerth, 1966; Browning and Mankin, 1966; Kabler, 1962).

***Recommendation 2–4:* Information should be obtained concerning the distributional pattern of the several strains of *Clostridium botulinum*, with particular emphasis on the prevalence of the various strains in foods.**

A considerable body of literature has been written concerning *Clostridium botulinum*, especially strains A and B. Recently a botulinum E strain has been incriminated in canned tuna and packaged smoked fish, and psychrotrophic strains of *Clostridium botulinum* B have also been observed; the role of these organisms at low temperatures is largely unknown (Ecklund, *et al.*, 1967). Since the spores can survive at 3.5°C and are toxinogenic at temperatures not thought possible for mesophiles, their recoveries from river beds, estuaries and bays take on added significance. Analysis of prevalence of these organisms by geographical distribution in the latitudes where these organisms are prevalent is of especial interest to man (Pivnick and Thatcher, 1968; Frazier, 1967; Ingram and Roberts, 1967; Ecklund, *et al.*, 1967).

***Recommendation 2–5:* More accurate reporting of food and water-borne illnesses (food infections and toxemias) should be required.**

The usual data on food and water-borne illnesses are those provided voluntarily and are almost wholly dependent upon the degree of concern of health departments in the individual states. The inadequacies of this approach are well illustrated by the fact that two or three states report almost all of the salmonelloses in the United States. As a result, accurate data on the prominence of this food-borne infection are not available.

Although reports from the National Communicable Disease Center have been of value, the lack of adequate morbidity data is undoubtedly a major reason for the downgrading of the problem of food and water-borne illness and for the lack of concern by decision makers (budget officials, health and welfare administrators, and political leaders) in seeking corrective action. This cycle can only be broken by a reasonable effort to achieve better reporting. Something better than that which now exists is essential. An appropriate program to meet this need should be carefully planned and placed in operation at the earliest possible date.

B. Mechanisms

Research on mechanisms concerns itself with the basic process of infection, host selection, and pathogenesis as well as resistance of bacterial, fungal, and viral agents in food and water. This area of study includes defining the relationship of these processes to the action of other agents (such as other organisms, chemical or physical factors) in the health and welfare of man.

Recommendation 2–6: **Information should be obtained concerning the manner in which *Proteus spp., Pseudomonas spp., Clostridium perfringens, Bacillus cereus,* and other organisms become invasive.**

Many food-borne outbreaks have occurred in which classical food pathogens could not be identified. As a rule, however, the total count of such organisms as mentioned above, which occur widely and are generally considered to be saprophytic, has been high. The mechanisms of apparent opportunistic (conditioned) pathogenesis is fundamental to a better understanding of their relationship to human health. Formation of histamine and tyramine and their deamination in the intestinal tract have been elucidated and the enzymatic formation of phosphoryl choline has been suggested. The formation of other compounds that may be toxic to man requires further study. Studies of mechanisms should include the possibility of synergistic interaction between two or more organisms to produce the pathologic effect (Mossel, 1968).

Recommendation 2–7: **Study is needed to determine why some serotype species (and certain members of the same serotype species) multiply in the tissues of various host animals, while others require a specific host.**

Salmonella contamination of foodstuffs is a widespread problem. Because of this organism's ubiquity, the traditional reliance upon indicator organisms is in doubt. It is generally recognized that certain isolates of *S. typhimurium* are highly invasive and are pathogenic to a variety of domestic animals and man, while *S. pullorum* is much more species specific. There are over 1300 serotype species of *Salmonella,* and the incidence of disease due to *S. typhimurium* alone represents 20 to 35 precent of the salmonellosis reported in this country. Studies of the invasive mechanisms that would explain differences in pathogenicity would enable public health microbiologists better to understand the health significance of specific situations (Prost and Riemann, 1967).

Recommendation 2–8: **Studies should be conducted on the microenvironment which promotes toxin production by staphylococci in foods.**

Particular emphasis should be on determining the conditions that cause staphylococci to poison foods and to be infectious.

Toxin-producing staphylococci represent one of the most obtrusive hazards to our food supply. These organisms are readily transmitted from animal to man and from man to man. While an estimated 30–50% of the population are stated to be carriers of toxin-producing staphylococci, the factors that lead to the establishment of this carrier state are unknown (Casman, 1965).

Recommendation 2–9: **Investigations should be made of the mode of pathogenicity of *Entamoeba histolytica*, i.e., its mechanism of invasion and the development of resistance of the host.**

Definitive evidence of the mechanism by which *Entamoeba histolytica* penetrates tissues is lacking. Little is known concerning how resistance to amebiasis is acquired. *E. histolytica* is a very important organism in any consideration that involves the conversion of waste water into potable water (Shaffer, *et al.*, 1965).

Recommendation 2–10: **Studies are needed on the relationship of nitrate-reducing intestinal bacteria to infant methemoglobinemia.**

The Public Health Service drinking water standard for nitrates plus nitrites (10 mg/l as N) is subject to question and requires confirmation. Extensive use of ammonia fertilizers is resulting in increasing concentrations of nitrates in ground waters underlying agricultural areas. Part of this basic problem is the microbiological aspect. Denitrification—and nitrification—in the environment is primarily a microbiological function. The objective of this recommendation is to clarify the microbiological role (Alexander, 1967).

Recommendation 2–11: **Studies should be conducted on the identification and behavior of antimicrobial agents that are intentionally or incidentally added to foods. Such studies should include research on the effects of these agents on food composition.**

Microorganisms produce antibiotics and/or bacteriocidins, some of which have received serious investigation in terms of their contribution to improving human and/or animal health. Also, attention has been directed to the elimination of undue residues of certain of these agents in food due to (a) the possible evolution of resistant strains and (b) the possibility of sensitization. However, both the antibiotics and bacteriocidins exist widely in nature and significant amounts of both may be consumed unknowingly in foods, such as cheese, sauerkraut, and fermented beverages and sausages. Presumably, these agents provide protective mechanisms that enable the elaborating microorganisms to exist in their native environment. Little is known concerning the contribution of these antimicrobial agents to the wholesomeness of the food in question. For example, does the nisin elaborated by streptococci prevent growth of *Clostridium botulinum* and *C. perfringens* in pasteurized (conserved) ham and, if so, is this mechanism of value in avoiding botulism or perfringens poisoning in such meat products? What is the nature of the activity of competing mold growth *Scopulariopsis spp.* that prevents *Aspergillus flavus* from producing aflatoxin in mold-ripened sausages (Kafel and Ayres, 1969)? Some antimicrobial agents may prevent the proliferation of spoilage organisms which cause changes in organoleptic properties that warn the consumer of a deteriorating product while permitting other organisms to grow and produce changes of unknown health significance. For example, antibiotic-treated fish may not develop characteristic odor or flavor changes, whereas other chemical indices of decomposition, e.g., free fatty acids, may increase.

C. Evaluation of Technology

A vigorous and continuing evaluation of technology in food and water processing in regard to microbiological hazards is required in order to a) develop microbiological reference specifications for new technology, and b) to develop appropriate techniques for the monitoring and surveillance of these processes.

Recommendation 2–12: **Basic research should be conducted to determine the microbiological, chemical and physical criteria necessary for establishing sound health guidelines for the reuse of waste water and for the national water pollution control programs.**

Waste water reclamation techniques of considerable promise have been developed that produce water of a quality which meets drinking water standards. However, the lack of basic guidelines for protecting the public from health hazards associated with this source of water precludes use as a domestic supply. Furthermore, improved health guidelines are needed in connection with the national water pollution control program.

Recommendation 2–13: **Veterinary inspection alone is incapable of adequately protecting against infections of animal origin. A new body of knowledge must be developed so that contamination by viruses and other organisms of animal origin, such as *Coxiella, Brucella, Salmonella, Shigella, Trichinella,* and *Taenia* can be detected in food products.**

At least thirty diseases are considered to be transmissible to man through meat, milk, poultry, eggs and other products derived from food-producing animals. Increase of populations exposed, widely distributed contamination of the environment, rapid transportation of both animals and foods, increased density of animal populations for both feeding and processing, and changes in food habits and in processing techniques all have in many ways increased the potential hazards posed by diseases of animal origin. A considerable body of information concerning these organisms relates to their effect on the animal itself (Sadler, 1968). Yet the importance of foods as vehicles of disease transmission remains. While the importance of these organisms is well recognized, ordinary treatment procedures do not take into account the chlorine resistance of the viruses, the temperature resistance of *Coxiella*, the hazard that *Brucella* presents to meat plant workers, the sporadic presence of *Salmonella* in exotic materials, such as food dyes, pharmaceuticals, candy, etc., the recognition that *Shigella* may pose special monitoring problems, the necessity of cooking pork rather than eliminating *Trichinella* at the source, and complete dependence upon clinical manifestations for detecting *Taenia* and several of the other pathogens. All of these limitations indicate that more work is needed for an adequate program of disease control.

Recommendation 2–14: **The development of a rapid and convenient methodology is needed to evaluate the microbial hazards of conventional and new methods of food processing.**

It is virtually impossible to eliminate all potentially dangerous organisms in foods. Many of the traditional foods and food manufacturing processes have been subjected to detailed analysis and, as a consequence, their safety can be reasonably well assured. However, a multitude of ready-to-eat foods have been introduced during the past decade or so. Little time elapses following the successful market trial of a product and its widespread appearance in markets from coast to coast. Many of these newer products and manufacturing techniques have been subjected to little analysis and have been on the market or employed for so short a time that the assessment of their safety on the basis of use experience cannot be made. Risk is associated with deviation from a recommended procedure as a result of mechanical or human error. Also, there are a few situations in which the intrinsic risk, (e.g., from mildly processed foods, plastic packaging of non-sterile low-acid or neutral products having sufficient moisture content to allow microbiological proliferation, or extension of shelf life of poultry or fish by means of antibiotic treatment) is sufficient to cause concern. It is stipulated on the label of some of these foods, in print difficult to read, that they be kept at low temperatures and sold or consumed within certain expiration dates. The merchant and the housewife are expected to abide by these precautions; unfortunately, all too often they do not. Products are merchandised quickly in large quantities and any methods applied, either for monitoring for evaluation, must be both rapid and reliable. It is at this point that many bacteriological tests fail or require either long periods of time or highly skilled personnel for their interpretation. The development of rapid, convenient methods is of paramount importance and should not be neglected on the presumption that this will be handled by the industry itself. When adequate monitoring methods become available, their use should be mandatory.

Recommendation 2–15: **Studies are needed on the preservation of biologically and chemically safe potable water in distribution systems. A new methodology is needed for evaluating potential hazards of new materials, water additives and technological developments in construction, inspection, and operating practices.**

Rules for the acceptability of materials, construction practices, inspection and maintenance have evolved slowly. Organizations, such as the American Water Works Association, American Society for Testing and Materials, and the National Sanitation Foundation have taken a role in developing criteria of good practice—particularly with respect to physical and chemical properties of materials. Recent developments and proposals include, among others, a variety of new thermosplastic materials, pipe pushing installation techniques, TV inspection, and computer automation of distribution networks, as well as dual water systems. A methodology for evaluating the potential health hazards of these interrelated developments is needed (AWWA Standards; NSF, 1966).

Recommendation 2–16: **Intensive research should be undertaken on a) the production of safe water from waste water; b) techniques for the reduction or elimination of microbial agents in waste water; c) the effectiveness of conventional and new water treatment processes on enteric viruses; and d) factors relating to the production and control of tastes and odors in water.**

The management of waste-waters, primarily of municipal and industrial origin, has traditionally been concerned with the removal of pollutants in order to minimize pollution of the nation's water resources. A new concern has been the total renovation of waste-waters in order to conserve water resources. In both cases the control of microbial agents exerts a controlling influence on man's use of water, either in the natural state or through municipal systems (e.g., recreational and bathing use in natural waters; drinking water in municipal systems). Additionally, the control of selected chemical agents (e.g., nitrates, sodium) in water renovation processes needs to be given consideration since these are important to human health and to the potability of the drinking water supply.

Studies so far conducted on water treatment processes and epidemiological experience suggest that conventional water treatment processes are effective in coping with the virus problem. However, the virus technology used in these studies is recognized as deficient and pursuance of definitive studies must await improved methodology. Water-borne pathogenic viruses remain a matter of concern (Walton, 1961; Clarke, *et al.*, 1964; Kabler, 1962; Kabler, *et al*, 1961; Green, *et al.*, 1968).

Tastes and odors continue to be the most troublesome problem of the waterworks industry. Consumers of water with bad tastes and odors frequently turn to other sources of potable water which may be of questionable sanitary quality. The presence of tastes and odors derived from algal metabolism suggests the possible presence of other substances with other physiological activities such as the toxic components of blue-green algae. Research on water quality should include studies of methods for the removal of tastes and odors. Such methods may also be effective in removing other undesirable components (U.S. Dept. of Interior, 1968; Fogg, 1965).

III. Health Aspects of Chemicals in Water

All natural waters contain a variety of substances in addition to the burden of chemicals that man's technology is releasing. Since chemicals reach man through air, water, and food, any measure of the challenge to the human organism must consider all routes. From the standpoint of health, it is the total intake that is important. The need for awareness of specific chemical species involved should be emphasized. For example, the inorganic arsenic that occurs in water is far more accessible to the human organism and its biologic processes than the organically bound arsenic in shrimp.

Tremendous strides have been made in recent years in analytical methods. However, further development of analytical techniques, especially those relating to routine control operations, is still required. Such control should be exercised before the deleterious effects are demonstrated in the human population. If man awaits epidemiologic confirmation, the situation may well become unmanageable (Dubos, 1966).

Recommendation 2–17: **Methods for the concentration, separation and identification of organic chemicals in water supplies need development. These compounds exist in extremely dilute concentration which makes it difficult to obtain sufficient quantities for an assessment of their activity and health significance.**

Many concentration procedures have been developed by chemists and biochemists that have not been applied to the problem of concentrating dilute organic materials in water. These techniques should be evaluated for this purpose. Availability of suitable concentrates will enable a determination of their physiological effects as well as an evaluation of the effects of various water treatment processes on their removal. Some materials which enter waterways are known to be carcinogenic to test animals. Others may have a physiological activity of which we are currently unaware. The organic contaminants should be identified and the physiological significance of the concentrations found in the environment determined. Also, the physiological significance of the heterogeneous mixtures as they exist in water should be evaluated.

Recommendation 2–18: **Further information should be obtained with respect to the biological significance of a number of elements and groups of elements in water. Particular attention should be paid to cadmium and nitrates. Such studies should include further epidemiologic investigations to (a) verify the linking of environmental cadmium (food, air, and water) to hypertension of renal origin; (b) elucidate the relationship of methemoglobinemia in infants to the content of nitrates in water; and (c) determine the validity of the observed correlation between cardiovascular disease and drinking of soft water. If, in the last case, a relation exists, the factor(s) in soft waters contributing to the disease or those in hard waters that may be exerting a protective influence should be identified.**

Schroeder (1965) reported a higher frequency of renal hypertension among people in which there was either increased amounts of kidney cadmium or increased ratios of kidney cadmium to zinc. The findings in man were similar to results in animals (Schroeder, 1964). Drinking water and beverages in contact with cadmium-containing galvanized containers and in food grown on soil containing cadmium derived from superphosphate fertilizers are considered chief sources of environmental cadmium.

Because of the extensive use of high nitrogen fertilizers in agriculture, the wider cultivation of nitrogen fixing crops, intensive animal husbandry and the large contribution from decay of vegetation, a rise can be expected first in nitrate in ground waters, and later in surface waters. Already, some ground waters exceed the federal drinking water standard. Infants up to six weeks of age are the principal population at risk. The possibility of chronic effects of subclinical methemoglobinemia on infants and young children also deserves attention (see also Recommendation 2–9).

Schroeder (1960) reported a very high negative correlation between consumption of hard water in the U.S.A. and death rates from cardiovascular and coronary heart disease, i.e., soft water was associated with higher death rates. Subsequent studies in England and Canada appear to verify that a "water factor" is associated with vascular disease death rates.

Recommendation 2–19: **Analytical instrumentation to maintain surveillance of drinking water supply sources should be developed to insure against contamination by toxic industrial chemicals. Vigilance should be maintained to identify the types, amounts and toxicologic potential of industrial chemicals frequently finding their way into drinking water supplies. Drinking water standards should be extended to provide for inclusion of existing and newly identified chemical agents on the same basis as for biological agents.**

IV. Non-food Uses of Water

The non-food uses of water comprise a heterogeneous group of applications (in contrast to water used for drinking purposes or as a component of food). The boundaries of the non-food use category are difficult to define precisely since environmental agents in water considered a non-food source can be transferred (e.g., through the food chain or through residues) into a food source.

For purposes of this section, the non-food applications of water are defined to include selected uses within the four categories of domestic, municipal, industrial and agricultural operations. The use of natural waters represents another category, within which are considered uses of water for such purposes as recreation, fishing, swimming, and bathing. The management of natural waters, the elements included in such waters, and the consequences of management are matters included in a final portion of this discussion.

The direct health implications resulting from the non-food uses of water are minimal for a number of uses (domestic, municipal, industrial, and agricultural) and are uncertain for others (swimming, bathing, and water recreation). The health-economic and health-resources relationships are of indirect concern, at present, but may become of increasing importance in the future. In considerations about allocation of resources, the health agencies should have the responsibility and authority to deal with these questions.

Recommendation 2–20: **In the realm of domestic use, research programs are needed to study obstacles (e.g., financial and organizational) to the utilization of environmental services (e.g., water supply, waste-water services) necessary for public health protection and convenience. In the realm of municipal use, encouragement should be provided for research programs concerned with alternative environmental services (e.g., dual water supply systems, innovations in waste water systems) that heretofore were not considered desirable or were technologically impractical.** The technical capability to provide a water supply adequate for personal and public hygiene and safety and public amenities is well established. Cultural, economic and institutional factors are obstacles to the provision of adequate domestic supplies in the smaller communities and in migrant and selected minority populations.

The present practice of providing a single service for drinking water as well as other uses evolved when water requirements were much smaller and sources of good water were more abundant. Economic reasons dictate that increased attention be given to waste water system innovations in urban situations and to study of the technical feasibility of dual water supply services.

***Recommendation 2–21:* Research programs should be continued to elucidate the role of dissolved oxygen in water quality and factors which affect this role.**

Dissolved oxygen and its relation to water have been studied exhaustively as a natural phenomenon and in relation to waste treatment processes. The nature of emerging problems in the management of natural waters, the extension of new technology to water pollution control, and the need to reclaim water bodies may require new and significantly different approaches to the management of dissolved oxygen. Anaerobic water sources are much more difficult to make usable for human consumption than are aerobic sources (Symons, 1969).

Eutrophication represents another major problem in the management of natural waters. The causes of eutrophication have been identified and the eutrophic state of a water body can be determined, but only in general terms. The precise information needed to control the eutrophication process is not available. Decisions to reduce nutrients, often at high cost, are acknowledged to be aimed at slowing rather than reversing the process.

***Recommendation 2–22:* A technology intelligence program should be established to forecast the rate of use and the probable effects of new chemicals, industrial materials or other substances at an early point in their development and use.**

Environmental control efforts have been characterized by "being concerned after the fact." A major need is the development of early intelligence to forecast future events and their effect on health (See Chapter 10).

***Recommendation 2–23:* Greater emphasis should be given to research programs concerned with recreation as a human need resulting from population growth, urbanization, mechanization and crowding.**

Natural waters (rivers, lakes, estuaries and reservoirs) are used for recreation, fishing, swimming, bathing and boating. For the purpose of these uses, natural waters are arbitrarily defined to include swimming pools.

The health hazards associated with the non-food use of natural waters in relation to recreation are in one case indirect and in a second case, uncertain. For the first case, the absence of aesthetically pleasing recreational waters tends to minimize the opportunities for wholesome outdoor recreation (U.S. Dept. of Interior, 1968). The uncertainty of the second case relates to the degree of illness incurred by persons as a result of the exposure of eye, ear, nose and throat

(EENT) during swimming, diving, and exposure to water pressure and the water environment (Stevenson, 1953).

Recommedation 2–24: **There is a need for a greater research effort on the relationship of human health to microbiological water quality. This should include studies of the health of the eye, ear, nose and throat in relation to swimming and bathing.**

Studies of swimmers fail to incriminate intestinal illnesses but do demonstrate gross effects on the EENT system. These studies also show that the highest EENT infection rates are associated with swimming pools as opposed to natural waters, but bacteriological studies fail to confirm that bacteriological quality of the water is the definitive factor.

Recommendation 2–25: **Greater research effort should be directed to problems on the control of schistosomiasis.**

In the United States and Puerto Rico two forms of the family Schistosomatidae are endemic. In Puerto Rico the disease is the type causing severe systemic effects.

In the United States, the disease is in the form of the much less virulent "swimmers itch". In all cases, eggs are transferred from feces (or in one species, urine) to the water environment which is the habitat of the snail host. Cercaria produced by the snail invade the human host through the skin. Management of the water habitat for control of the snail host has proven to be a very difficult task. Chemotherapy has been utilized in control programs but adequate programs remain to be developed.

Recommendation 2–26: **Basic studies are needed on the chemical quality of marine, estuarine, and fresh waters in relation to the growth, physiology, and toxicity of aquatic organisms. Such studies should include toxic blue-green algae of fresh water, dinoflagellates and "red tide" organisms, paralytic shellfish poisons, and objectionable aquatic plants.**

There may be considerable public health relevance in the ecologic relationships between microorganisms. Thus, in mixed populations, there can be mechanisms that prevent the development of virulent, pathogenic organisms. Much more needs to be known about these ecologic relationships.

A high priority is given this recommendation because of the belief of the Subtask Force members that too few workers are involved in this area of research and because of indications of increasing reliance by the world's population upon sea resources for the production of protein. Even today there are examples (such as Alaska) where the potential development of vast sea resources (specifically the harvesting and marketing of clams) is restricted because of problems of toxicity.

The area of research envisioned is very broad and is conceived as extending to programs such as those concerned with the management of excessive growths of aquatic plants. In the case of toxic shellfish, the poisons vary with geographical location and time of year and are apparently relatable to environmental conditions (i.e., water quality). The poison formers include all types of marine life ranging from dinoflagellates through shellfish to marine fishes.

Such poisons as ciguatera, scombroid, parayltic shellfish poison, and that of the puffer, among others, have been widespread and the cause of innumerable cases of food poisoning and many deaths (McFarren, *et al.*, 1960).

V. Non-nutrient Components of Food

The chemical entities included under this heading encompass a wide spectrum of substances that are introduced into foods through a number of routes. Such substances may be categorized into two groups: (1) those added by man in the course of food manufacture or preparation; (2) those present as naturally-occurring components or contaminants.

The first category will be referred to as "food additives and residues". In this group, some compounds are added directly to foods or are produced in food by the application of various forms of processing. Also included are those components of foods that arise as residues from seed, soil or crop treatments; as residues of drugs or other additives fed to animals; or from migration of packaging materials into foods. Estimates of the number of compounds included in the food additive and residue category vary, but a figure of 10,000 is probably conservative. Of the food reaching the U.S. consumer, about 95% has undergone some form of processing, and the average annual per capita consumption of intentional food additives has been estimated at 1.5 kilograms.

As a toxicological consideration, the breadth of this field makes it difficult to single out individual substances or even groups of related compounds for attention. The use of many additives and forms of food processing goes back for centuries. A considerable number of common and widely used additives have been introduced in the last twenty-five years. In fact, a few of the most recent have as yet achieved acceptance only in certain countries. This is due only in part to doubts about their safety; where official policy maintains the shortest possible list of additives, a new compound—whatever its merits—may be rejected on the grounds that the list already contains an additive serving the same technical purpose. In countries without these restrictions, the benefits of continued proliferation of new additives must be evaluated in the light of the burdens placed upon scientific manpower and resources required for their safety evaluation.

Stemming from these very different backgrounds, the bases of acceptability for safe usage vary widely. At one extreme are those compounds or products that are accorded "generally recognized as safe" (GRAS) status on the basis of long-established use without evidence of harm to the consumer. At the other extreme are the relatively few food additives accepted for specific and limited uses, their acceptance based on results of investigations that meet modern standards. The majority of additives are permitted for use on the basis of data that were considered adequate at one time, but now must be ranked as "preliminary".

Only a portion of food additives and residues have been studied thoroughly enough to meet exacting, present-day standards. On the other hand, many food additives and residues have a long history of apparently safe use. It is clear that untoward effects stemming from food additives and residues are exceedingly difficult to recognize or even establish with any degree of certainty once suspicion has been aroused. Consequently, in view of the large numbers and amounts of compounds involved and the contribution made by them to the chemical background to which populations are exposed, every effort should be made to re-examine and update the safety evaluation of all such compounds at regular intervals.

A somewhat different set of problems is posed by the second category of non-nutrient components of foods, the naturally-occurring toxicants and contaminants. The number of compounds in this group is not precisely known. The existence of these compounds is usually recognized because of overt toxicity or diseases associated with their presence in animal feeds or in human foods. Because of the circumstances under which they enter the food chain, these substances probably pose differing degrees of risk to public health in areas with different agricultural technologies. On a global basis, exposure of human populations to some naturally-occurring toxicants and contaminants probably varies inversely with the level of technological development. It is becoming clear that certain types of these substances can be widespread in major food commodities and can occur in foods under unanticipated circumstances.

From a chemical standpoint, the naturally-occurring food contaminants and toxicants represent a great diversity of organic molecules. Illnesses associated with their ingestion are also of diverse character, but can be grouped into two broad types for convenience of discussion. Exposure to the toxic agents may consist of (a) brief exposure to high levels and/or to highly potent toxins with acute poisoning, or (b) prolonged intake at low levels, with no overt signs of toxicity. Thus, different kinds of risks are involved by virtue of the nature of the biological activity of the toxicants, the levels at which they occur in foods, or the amounts of foods containing them which are consumed. Because different risks are involved, research requirements for solution of the problems vary.

Numerous examples of naturally-occurring toxicants could be cited. A few of these have been specifically associated with human illnesses. Acute, sometimes fatal, illnesses associated with seafood toxins are among the most dramatic examples. There are also examples of human illnesses caused by toxicants or contaminants present in food of plant origin. Such syndromes as lathyrism, favism, cyanogen poisoning, and ackee poisoning generally occur in localized areas and populations. Although many of these syndromes have long been recognized, the causative agents and their mechanism of action have yet to be elucidated.

Assessment of the health hazard posed by chronic exposure to lower levels of toxicants and contaminants is more difficult. With few exceptions, these problems have become recognized by means other than their direct association with human illness. Usually, recognition has resulted from adverse effects in animals and evaluation of their significance to man involves extrapolation of these observations to man. The potential health hazards posed by such substances must be evaluated in terms of such factors as the probability of their biological effects and the seriousness of these effects.

Comprehensive surveys reveal a vast array of chemical entities encompassed by the compounds added to foods by man, food additives and residues, and occurring as natural toxicants and contaminants. Consideration of this broad range reveals many problems of potential public health importance requiring further research effort. Based upon the criteria outlined above, we have identified a number of problems and areas that stand out as those requiring further attention with priority, while recognizing that many other important problems exist. These areas form the basis for the following research recommendations:

> ***Recommendation 2-27:*** **The contributions that food chemistry can make to toxicology should be greatly encouraged and developed. Foods are exceedingly complex mixtures when viewed as chemical systems, and studies on their chemistry require unusual expertise. Considerable expertise already exists in some areas, such as flavor chemistry and reaction chemistry, but research on these topics has been traditionally oriented toward objectives other than food toxicology. The Subtask Force recommends that efforts be made to encourage the orientation of food chemistry research activities toward the possible health implications of non-nutrient components of foods.**

In the context of environmental health, knowledge is required, in particular, of topics such as the interaction between food additives and residues and other food constituents; of the composition of ill-defined additives (some of which are in wide use); of the chemical nature of the non-nutritive components of foods; and of the chemical changes brought about by cooking and other processing of foods. This is not to suggest a cataloging of minor components of foods. Rather, it is to recommend that experienced food chemists be encouraged to apply their talents to specific problems of health interest. For example, much effort by flavor chemists has been devoted to analysis and characterization of smoke constituents, exclusively from the point of view of organoleptic properties. The possible health considerations (e.g., in induction of stomach cancer) of these same (or other) smoke components has not been taken into account in research planning.

Another example is the possible formation of biologically active compounds through processing. It has been suggested, for example, that N-nitroso derivatives (which may be carcinogenic) could form in foods under certain conditions of processing. The attention of expert food chemists will be required to conduct studies in this area.

This fundamental information will be of value in discovering biologically active substances originally present in foods or generated by modification of food ingredients. There is particular concern over the possibility of formation of substances that induce or modify carcinogenicity, substances capable of bringing about sensitization, or those causing other forms of intolerance. In all such circumstances, it is important to clarify the mode of formation of the compounds involved and to elucidate the mechanisms by which they bring about their biological effects.

Recommendation 2–28: **Research into all aspects of nitrates and nitrites and N-nitrosamines present in food and water should be undertaken.**

In addition to acute effects such as methemoglobinemia (see Recommendations 2–9 and 2–17) mounting evidence for the possible formation of N-nitroso compounds in foods containing nitrates-nitrites warrants a detailed investigation of all aspects of the problem. Substances containing the N-nitroso configuration comprise a chemical group of which many members are known to be potent carcinogens (Magee and Barnes, 1967). They are multipotential carcinogens in animals, causing tumors in many tissues, and have a high order of potency (Druckery, 1967). These compounds can be formed through a number of routes, as for example by microbial synthesis and through interactions of nitrites and secondary amines. They could readily form in foods containing their precursors and may, therefore, be widely distributed when the necessary precursors and conditions are present. The possibility of their formation ***in vivo*** when both nitrites and the secondary amines are present should be investigated (Sander and Burkle, 1969).

Recommendation 2–29: **An intensive research effort should be undertaken on the evaluation of both the acute and long-term effects of mycotoxin contamination in foods. This is in addition to the extensive investigations already in progress on the known mycotoxins such as the aflatoxins.**

Implications of the presence of mycotoxins in foods have not been adequately studied from the standpoint of epidemiology, qualitative and quantitative analysis of levels of exposure, and exploration of the multitude of biological effects that could result from their presence.

Recommendation 2–30: **Additional research efforts are needed on seafood toxins, alkaloids and glycosides, pressor amines and other naturally occurring pharmacologically active substances in foods. Specific areas requiring attention are (1) the chemical and pharmacologic properties of seafood toxins, as well as more definite information on the general biology of poisonous marine forms; (2) alkaloids and glycosides in common foods, as well as in herbal medicines, bush teas, etc., as related to their capacity to produce acute and chronic effects; and (3) the health effects of pressor amines present in foods, or produced in the intestine.**

An extraordinary variety of toxic substances can be present in foods of marine origin. The likelihood of increasing dependence on these as a source of food makes it imperative that the field be thoroughly investigated.

Alkaloids are regularly consumed by vast populations in various foods in which they are normally present. In many parts of the world, highly toxic and potentially carcinogenic alkaloids are regularly ingested by children as well as adults in herbal remedies, bush teas, and similar decoctions. Evidence is mounting of an implication of pressor amines in migraine and other disorders. Particularly those amines related to the aromatic amino acids, phenylalanine, tyrosine, tryptophan, and histidine (i.e., histamine, tyramine, tryptamine and other metabolites such as serotonin and norepinephrin) are known to exist naturally in animal tissue, cheese, sauerkraut juice, wine, tomato, pineapple, banana, paw paw, and passion fruit (Strong, 1966). There is also the question of the part played by the intestinal flora in generating toxicants from food ingredients or additives. Do these substances exist in the natural commodity as inactive conjugates? If so, how is the active principle released and under what circumstances is the amine absorbed from the gut? It is known that disastrous consequences would result if these amines were administered intravenously in concentrations equivalent to those occurring in normally consumed quantities of these foods.

VI. Agricultural Chemicals

Chemicals of great variety and complexity are manufactured and used by man. The methods of manufacture and use inevitably result in situations whereby man may be exposed through air, food, and water. The escape of chemical contaminants may be inadvertent or deliberately allowed as in the case of pesticides and fertilizers. In most instances, a considerable amount of information on the toxicology of these compounds has been obtained by research and by experience. The evidence thus obtained indicates few, if any, instances of immediate health hazard to man under recommended conditions of use. However, knowledge is not adequate with respect to chronic and indirect effects of pesticide use. It is especially important that research on possible long-term effects on intact animals and successive generations be pursued. Such research should be directed to problems of microsomal enzyme induction and other effects which may be more indicative of exposure than of deleterious health effects, as well as to biochemical alterations which might be correlated with the health or performance of man.

Recommendation 2–31: **Research is recommended on the effects of long-term, low-level exposure to pesticides including the biochemical, physiologic, psychobiologic, and epidemiologic aspects. This should include investigations of: (1) The interrelationship among pesticides, nutrition, and environmental stressors to evaluate the potential direct or contributory hazards. (2) The efficiency of uptake by test organisms including man at various levels of exposure to pesticides from food, water or other elements of the environment. (3) The mass balance of the material ingested to that retained, the amount metabolized and the quantity deposited in various tissues and fluids.**

Pesticides are representative of classes of organic chemicals commonly used by man, selected specifically for their biological activity. Their use on large areas exposes other components of the environment to contamination. Evidence exists that nutritional status may modify the biological effects of many chemicals and in other instances expressions of effect are delayed until the organism is otherwise stressed by cold, food deprivation, illness and other factors.

Although great efforts have been expended to measure the level of residues in food stuffs as a route of ingestion of pesticides, less has been done on levels in water and considerably less on exposure through other media. Very few studies have been attempted to quantify the total amount of such residues retained by the organism upon exposure through food or other avenues of intake.

Metabolism and excretion represent major defense mechanisms against chemical challenge. Knowledge of these factors helps to provide a reasonable estimate of innocuous levels of exposure.

It will be necessary to continue to use pesticides for protection of man's health and production of his food to meet the needs of a growing population. For this reason, toxicity of agricultural chemicals will continue to merit attention. It may be pointed out, however, that studies on pesticides are valuable not only because they contribute information on these compounds, but also because the enlarged knowledge of the toxicology of pesticides can be a valuable resource in dealing with the toxic effects of industrial and waste compounds of similar nature (Brady, 1967; Mrak, 1969; NAS/NRC, 1966 and 1969).

Modern crop production demands extensive use of fertilizers. Not only may the manner of use of these materials result in some accumulation of the fertilizer element in foods, but possible traces of other elements accompanying them may be a health factor. In some instances the presence of a given material in trace amounts may be beneficial, but in other instances it may pose health problems. Little attention has been directed either to the kinds and amounts of materials that may be found in fertilizers and subsequently picked up by food or from the irrigation water used on crops. Such water could receive chemicals from other treated areas by extraction of natural deposits and subsequently add these to the fields and crops being irrigated. Similarly, with the growing use of reclaimed water, attention must be directed to the burden of chemicals that this water may carry and transfer to man through his crops. Such waters carry not only nitrates from fertilizers, but trace substances, pesticides, and other organic chemicals, and in certain areas, radionuclides. It would thus be possible for substances such as cadmium, chromium, copper, various metals from metallurgical plant waste, and a host of organics to become residues in food crops through either fertilizer or soil.

Recommendation 2–32: **A program of investigation should be undertaken to evaluate trace contaminants with known health implications which may be introduced into foods by fertilizers and irrigation waters. The latter portion of this study should include an evaluation of the role of reused or reclaimed water as a carrier of trace amounts of various minerals and organic substances such as pesticides.**

There is suggestive evidence that trace amounts of certain substances may influence the health of man. These trace substances may be introduced into fertilizers through the raw materials used and the manufacturing process, and then into foods and water. A distinct possibility also exists that water can become contaminated by various minerals which are not removed in the usual treatment processes. Similarly, so-called natural waters may pick up a burden of such materials by influx into surface and ground water or by extraction from deposits. This water, subsequently used in irrigation or for other purposes, could result in an exposure of man to potentially noxious agents.

VII. Chemodynamics

Literally thousands of chemicals are mined, manufactured, and used by man. Inevitably, in the processing or use of these chemicals, some escape and become environmental contaminants. In other instances, a chemical may be deliberately applied in the environment as is the case with pesticides. The amount of chemicals escaping or being applied is estimated to run into the millions of pounds per year. Some of these chemicals are very short-lived in the environment, others, by virtue of their physical properties, may persist for a considerable time. In addition, radionuclides which are released take their place as environmental contaminants. Through a variety of as yet not completely understood processes, these chemicals may be transported from the point of release to a site wherein they become an exposure hazard to man. The ease of mobility and the amount of chemical transported depend not only on the transport mechanism itself, but also on the properties of the compound and the amount released. Thus, chemicals may contaminate the home or factory in which they are used and may result in widespread exposure to man either directly or in his food and water. In some instances, such substances become incorporated in the food chain, often with resulting magnification of concentration affording an even higher level of exposure. Unfortunately, these matters have received all too little investigation. For these reasons, the Subtask Force believes problems involving the kinds and amounts of chemicals released into the environment, their transport, behavior and the resulting exposure to man urgently require investigation.

> ***Recommendation 2–33:*** **Research is needed to (1) identify the kinds and amounts of stable and radioactive chemicals that contribute to the environmental burden; and (2) elucidate their physical and chemical properties and the effect of these properties upon their transportation and partitioning among the various environmental phases. This work should be designed to provide information on the identity of the agents, their source, their persistence and ultimate fate in the environment, and the development of analytical methods required for surveillance.**

Among identified environmental contaminants are organochlorine compounds from industrial as well as agricultural sources. It is probable that others are also present in the environment in measurable amounts, as evidenced by some preliminary data, but little research has been done to detect and identify the major portion of such chemicals. Application of new analytic methodology should permit identification and quantification.

Chemicals such as DDT, p-chlorobiphenyl and radionuclides are known to appear at great distances from points of release, clearly indicating their mobility. Partial explanations of transport on the basis of meteorology and hydrology can be afforded. However, more sophisticated knowledge is needed on the interrelationships of the properties of compounds and their interaction with the environment as factors in transport and partitioning. On the basis of known chemical composition of organisms and properties of compounds, for example, it has been possible to estimate the amount of chemical uptake from a given level of concentration in the environment. Further, the energy of adsorption on inorganic surfaces (particles) and proteins (biocolloids) have been shown to be related to readily measured properties of both the colloid and the chemical. From these data accurate predictions of environmental behavior and likelihood of exposure can be made (Freed, *et al.*, 1967; Cohen and Pinkerton, 1966).

Chemicals are broken down in the environment by a number of processes including those of a photochemical, chemical, and biological nature. These occur at varying rates depending on the nature of the chemical and the conditions. The products formed depend both on the process of breakdown and the chemical. Such degradation products in themselves may have health significance. Too little is known about rates of breakdown, material balance or reaction products. Data should be readily obtainable to permit accurate estimations of rates of breakdown and thereby rates of accumulation for specific products and product groups (Alexander, 1967; Nash and Woolson, 1967; Freed, *et al.*, 1967).

Lastly, little is known about the quantitative aspects of the biological availability and efficiency of partitioning of environmental contaminants into organisms. It is known, of course, that materials are partitioned across the organism-environment interface and subsequently are deposited in the tissues, but dynamics of this process are poorly understood. Thus, while it has been possible in some cases to estimate uptake from chemical data and to confirm this experimentally, much more needs to be known (Godsil and Johnson, 1968; Wheatley and Heartman, 1968).

Recommendation 2–34: **It is recommended that careful assessment be made of direct alterations in ecologic aspects of the environment as they bear on man's health and well being. Examples are an upset in the oxygen cycle and the nitrogen cycle or the interruption of the food chain that may be induced by environmental contaminants.**

It is becoming increasingly accepted that man's health and welfare are not only affected by direct environmental insult, but may also be influenced by ecological changes in the environment. Chemically induced changes may influence the oxygen supply and amounts of soluble nitrogen compounds to which man is exposed; they may encourage overgrowth of objectionable organisms, or the release or production of secondary toxicants (NAS/NRC, 1969; NAS/NRC, 1966).

It is of environmental health relevance to determine the kinds and amounts of chemicals arising from all sources that contribute to environmental contamination. There is need, also, to assess the total environmental burden of such contaminants and their distribution in air, water, soil and food chains. The objective of this work is to develop information based on physical and chemical principles on the nature and amounts of chemicals, mechanism of distribution and partitioning and the fate of these chemicals in the environment. By establishing these quantitative relationships based on the properties of the chemicals and the systems and mechanisms of transport, it would be possible to predict the probable exposure level and hazard to man and to develop appropriate preventive measures.

VIII. Summary

Few things have more influence on man's health than the food he eats and the water he drinks. Rapid technologic change, increased population, and greater concentration of people into urban centers are threatening to overwhelm the limited measures currently provided for protection against harmful agents in food and water. Earlier successes in controlling food and water-borne infectious diseases have resulted in complacency. Current microbiologic methods and understanding of pathogenicity are inadequate. Recent outbreaks of food-related disease in animals have emphasized the health significance of naturally occurring food components and underlined our ignorance of the non-nutrient components of ordinary foods. The unquestioning acceptance of the natural constituents of such foods as safe is based on relatively short term observations, albeit repeated many times during the course of man's history. Little is known either from the experimental laboratory or epidemiologic studies concerning the possible roles that our daily food may play in neoplastic and degenerative diseases.

To answer these questions, the Subtask Force recommended increased effort to improve the reporting of food- and water-borne illnesses and to improve analytical methodology for recognizing, characterizing and measuring microbiologic and chemical agents in food and water. Also cited was the need for the performance of supportive research to determine the mechanisms of the resulting biologic effects. Guidelines for this effort are specified in a series of recommendations for more accurate reporting of food- and water-borne illnesses (Recommendation 2–5) and for the development of rapid, reliable analytical and evaluative techniques for viruses, pathogenic bacteria, pseudomonads, and fecal streptococci in food and water, for organic chemicals in water, and for microbial and anti-microbial hazards of conventional and new methods of food processing (Recommendations 2–1, 2–2, 2–11, 2–13, 2–14, and 2–17). Other recommendations call for improvements in procedures for evaluating and gathering data on the distribution patterns of disease organisms (*Salmonellae, Shigellae,* and *Clostridia*) and their indicators in food and water (Recommendations 2–3 and 2–4), and on the mechanisms of action of organisms such as *Proteus spp., staphylococci,* and *E. histolytica* (Recommendations 2–6 through 2–9).

While certain trace elements in food and water are essential for life (and a deficiency produces disease), others are known to cause poisoning and any element is toxic if the dose is excessive. Because some trace element deficiencies are probably still unrecognized and many questions remain concerning the known elements ingested by man, the Subtask Force recommended increased research on defining the relationships of certain bacteria and chemicals to various disease conditions (Recommendations 2–10, 2–18, 2–24 and 2–28), and the impact of conventional and projected treatment processes and equipment on water quality (Recommendations 2–15 and 2–16). Also called for is research to develop improved procedures for the surveillance, control and maintenance of water supplies. Specifically, the Subtask Force urged that basic research be conducted to determine the microbiologic, chemical and physical criteria necessary for establishing sound health guidelines for the reuse of waste water (Recommendation 2–12), and that a study be made to find ways of removing financial and organizational obstacles to the utilization of environmental services (e.g., water supply and waste-water services) necessary for public health protection (Recommendation 2–20).

Other specific problems related to water quality and on which the Subtask Force recommended greater research effort included improvements in analytical instrumentation for surveillance of drinking water supply sources (Recommendation 2–19), the control of schistosomiasis (Recommendation 2–25), elucidation of the role of dissolved oxygen in water quality and factors which affect this role (Recommendation 2–21), and initiation of basic studies on the chemical quality of marine, estuarine, and fresh waters in relation to the growth, physiology, and toxicity of aquatic organisms (Recommendation 2–26).

In a broader sense, the Subtask Force called for the development of a program to forecast the rate of use and probable effects of new chemicals and other substances (Recommendation 2–22), and the placing of greater emphasis on research programs concerned with the recreational needs of people which result from population growth, urbanization, mechanization, and crowding (Recommendation 2–23).

The Subtask Force also urged greater effort on the evaluation of the acute and long-term effects of mycotoxin contamination and on biological toxins, and other naturally occurring pharmacologically active substances in foods (Recommendations 2–29 and 2–30). In addition, the Subtask Force recommended consideration of food toxicology in research now directed primarily to flavor chemistry and reaction chemistry (Recommendation 2–27).

Pesticides and other agricultural chemicals present special problems because they are generally biologically potent substances and are widely used. Since foodstuffs represent man's greatest source of intake of these materials, it is urgent that research on the effects of long-term, low-level exposure to pesticides be increased. Particular emphasis should be placed on biochemical, physiologic, psychobiologic, and epidemiologic aspects of such substances (Recommendations 2–31 and 2–32). The unexpected appearance of pesticide residues in fish from oceans and lakes and the increase in nitrates in certain natural waters indicate also the need to understand the chemodynamics whereby environmental contaminants are translocated from where they are used or liberated to where they may unexpectedly appear (Recommendations 2–33 and 2–34).

BACKGROUND DOCUMENTS

Document Number	*Author*	*Title*
FW–1	Wolf, H. W.	Microbiological Aspects of Potable Water.
FW–2	Stokinger, H. E.	Evaluation of the Toxic Potential of the Chemical Environment of Man—Water, Air, Food.
FW–3	Dworsky, L. B.	The Non-Food Uses of Water.
FW–4	Ayres, J. C.	Food Microbiology and Virology.
FW–5	Wogan, G. N.	Natural Toxicants and Contaminants in Food.
FW–6	Golberg, L.	Intentional Food Additives and Chemical Residues in Food.
FW–7:I	Freed, V. H.	Chemodynamics—Transport and Behavior of Chemicals in Environment.
FW–7:II	Freed, V. H.	Toxicology of Pesticides.
TX2–1:I	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part I
TX2–1:II	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part II
TX2–1:III	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part III
TX2–1:IV	Falk, H. L.	A Review of Syn-, Co-, and Anti-carcinogenesis.

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Chapter 3

INDUSTRIAL EXPOSURES AND CONSUMER PRODUCTS

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INDUSTRIAL EXPOSURES AND CONSUMER PRODUCTS*

I. Industrial Exposures

A. Introduction

Through the combination of skills of physical scientists and engineers on the one hand and biomedical scientists and physicians on the other, many significant principles for recognition, evaluation and control of health hazards from industrial exposures have been established. The first major tenet in recognizing and evaluating such health hazards is to demonstrate a quantitative relationship between a measured level of exposure to some agent in the environment and the degree of a significant response or health effect in the exposed population. Understanding of this dose-response relationship provides the basis for applying engineering or medical controls to reduce the exposure to levels below the response threshold. A basic assumption in the practice of industrial hygiene is that many can tolerate without health impairment exposures to hazardous agents at levels below the response threshold.

Application of these basic principles of occupational health has served to protect workers in hazardous trades from acute and chronic disability arising from exposure to the classical agents of occupational disease including fibrogenic dusts, toxic metals, carbon monoxide, carcinogenic agents such as tar products, organic solvents, and from physical stresses such as radiant heat and noise. The extent to which such problems still remain stems in many cases from failure to apply established control procedures. That preventive measures against traditional industrial hazards are not being fully employed in industry today will be pointed out in a succeeding section of this chapter.

Technological innovations constantly introduce new and potentially toxic chemicals and hazardous new forms of physical energy, but the hazards of acute effects from these new agents can largely be predicted through toxicologic evaluation. Thus controls can be implemented through advanced planning without first incurring costly effects on the workers' health. The risk of industrial skin allergies is an exception and cannot be anticipated by animal tests.

Differing in kind from the problems of controlling specific known agents are those in which etiologic relationships between a suspected environmental haz-

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* This Chapter was prepared by a Subtask Force chaired by Dr. David Minard and co-chaired by Dr. Harold C. Hodge. Others who assisted in its preparation included Drs. Arend Bouhuys, Edward R. Crossman, Philip E. Enterline, Theodore Hatch, Morris A. Lipton, and William H. Strain.

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ard and health effects in man are not clearly defined. Such problems include the chronic effects of environmental agents which may not be manifested by short-term health impairment nor be identifiable by clinical signs.

A related problem is that of possible health effects of exposure to known hazards, singly or in combination, at levels below the threshold for acute and recognizable response. In both problem areas, susceptible individuals may constitute a small fraction of the exposed population, and detection of the hazard requires highly sophisticated epidemiologic and toxicologic methods not presently applied to the evaluation of health problems in industry.

A problem of growing concern is the extent to which hazardous industrial agents may act to increase the prevalence or severity of chronic degenerative diseases. Industrial exposures might be conceived as producing impairment of the system as a precursor of disease, aggravating existing states of ill health, increasing the severity and duration of illness, or hastening terminal breakdown of the system. The basic causes of the disease may lie elsewhere, possibly within the individual himself, the industrial agent acting only as a contributing factor.

Another kind of industrial health problem just beginning to be recognized, but which may well loom large in the future, is related to hazards in the physical or social environment which impose stress on psychological systems of the exposed worker and are manifested not in biochemical or clinical responses but in decrement in skilled performance, perceptual capacity, or social adjustment. New systems of automated production through remote control relieve the worker of strains from physical effort and remove him from the proximity of chemical and physical agents involved in the production process. At the same time, new demands are imposed on him for mental alertness, sensory perception, decision making, and ability to make motor responses with speed and precision under emergency conditions.

Effects of work stress contribute, no doubt, to accidents and accident-prone behavior, to work absence, to alcoholism, to job turnover, and to social maladjustment on the job. New methods for detecting and controlling the health hazards which lead to these manifestations of psychological strain will require methods of assessment utilizing the skills of behavioral and social scientists.

B. Scope of the Problem

The labor force in 1967 (Manpower Report of the President, 1968) totaled 80.7 million people with 77.3 million in the civilian labor force. Of the latter, 49.0 million were male and 28.3 million were female workers. Agricultural workers constituted only 3.8 million. Of the 66.1 million non-farm workers receiving wages or salaries in 1967, those employed in goods-related industries numbered 27.5 million, and those in service-related jobs, 38.6 million. Present trends indicate the numbers employed in service-related jobs will increase, with a relative decrease in numbers of production workers. Although the proportion of workers in the upper decades of age will decrease, the actual number has increased in recent years to the 1967 total of 6.9 million within the age range from 55 to 64 years and 2.1 million 65 years of age and older.

It has been estimated that 15 million workers in industries with 500 or more employees are covered by some form of full-time in-plant health services while the remaining 62 million, working in industries employing less than 500 (including agricultural and migrant workers) are not covered by such services (Frye, 1966).

Frequency rates for occupational injuries reveal wide differences among various industries and occupational groups. Thus, the National Safety Council (1969) reports that the frequency rate in 1968 for disabling injuries (per 1,000,000 man hours) was 1.6 in the automobile manufacturing industry with a corresponding severity rate (days charged per 1,000,000 man hours) of 189. At the other extreme was coal mining with a frequency rate of 35 and a severity rate of 8,258. The mean frequency rate for all industries was 7.3 with a corresponding severity rate of 665. The total number of deaths from occupational accidents in 1968 was 14,300, with 2,200,000 disabling injuries.

Inadequate reporting makes it impossible to determine the incidence and prevalence of occupational diseases. The best reporting is in the State of California where such procedures are mandatory. By extrapolation of the data from that State, Dr. William H. Stewart, then Surgeon General of the USPHS, in his testimony before the House Select Sub-Committee on Labor (Hearings on H.R. 14816, Occupational Safety and Health Act, 1968) estimated that there are at least 336,000 new cases of occupational disease in the United States each year. The impact of non-occupational disease is indicated by data of the Bureau of Labor Statistics (1969) which reveal that, on the average, each worker is absent from work six days a year.

The prevalence of health hazards in small industries on a national basis is largely unknown. Basing his estimate on earlier regional surveys conducted by the Division of Occupational Health, the Surgeon General testified that 65% of 650,000 employees in 30,000 plants were found potentially to be exposed to toxic materials or harmful physical agents such as noise. A recent USPHS survey not yet released (Key, 1969) included a sample of 803 establishments employing 260,000 workers in the Chicago area representing a universe of 14,453 plants employing 1.5 million workers. In 95% of the plants there were no full-time or part-time in-plant health services. In 56% of the plants there were one or more known or suspected chemical hazards. In 23% of the plants, employees were exposed to one or more physical hazards (heat, noise, radiation, etc.). In 20% of the plants visited, employees were exposed to one or more dust hazards.

C. *Areas of Research Need*

Some areas of research on industrial exposures of unquestioned importance have been considered by the Subtask Force, but by deliberate decision have not been included for background study or for specific research recommendations.

The lung and skin are two of the major interfaces between the body and the environment. Respiratory exposures and subsequent lung disease are discussed in some detail. The response of the skin has not been dealt with in comparable detail, although industrial skin diseases exceed in prevalence and incidence all other occupational diseases combined.

Inflammatory responses of the skin to chemical agents constitute an important public health problem and a complex area of disease. Reactions to irritants include a wide variety of cellular and biochemical responses all of which are altered in turn by factors of the physical environment. Allergic diseases involving skin are dependent on both the nature of the molecular stimulus and the host's inherent immunobiologic response. Present methods of determining levels of allergenicity have practical usefulness but more dependable techniques of screening are needed. In both the irritant and allergic skin diseases studies of cellular and biochemical mechanisms of such reactions are also urgently needed. Research in these areas is appropriate for the NIEHS but also falls within the mission of the National Institute of Allergy and Infectious Diseases.

Toxic occupational exposures on occasion may also affect the liver, kidney, brain, blood, bone marrow, and other organs. No attempt has been made here to review systematically all of the specific toxic agents and their effects on individual organs or organ systems. Each target organ could serve as a topic for review similar to that undertaken for the lung. The discussion of the lung, which follows later, in a sense serves as an example of how research needs for studies of other organs could be developed.

Also deserving of comment are health hazards of agricultural workers which have also been omitted from detailed scrutiny by the Subtask Force. In this area, hazards of traumatic injury and of acute and chronic intoxication from agricultural chemicals are perhaps the two major health problems. Research needs in the latter case are for more basic understanding of the mechanisms of action and interaction of pesticides and related chemicals as well as their storage, metabolism, and elimination from the body. Research on methodological approches to these problems have been recommended by the Subcommittee on Toxicology (Chapter 8).

In regard to accidental trauma, the Subtask Force recognized an urgent need for behavioral studies in relation to accidents, particularly research on transitory impairment of mental functions which may increase risk of personal injury or increase hazard to public safety. It has also recommended research on the role of skill and experience in accident prevention. No attempt was made to identify other possible areas for accident research, for example, on human factors in safe design of industrial equipment and processes, personal protective devices, sociologic research on accidents, and so forth.

These disclaimers notwithstanding, the Subtask Force is satisfied that its recommendations for research, though not comprehensive, are of sufficient breadth and depth to encompass problems of industrial exposure which have major health significance and at the same time are clearly relevant to the mission of NIEHS.

D. Setting Tolerance Levels

The establishment of a tolerable level of exposure to a hazardous physical or chemical agent, below which man is capable of dealing with the imposed stress without significant health risk, is a fundamental need in the design and operation of practical control programs against environmental health hazards. That such levels exist finds considerable support in industrial experience over the past half century. Systematic reduction in levels of exposure to silica, lead, carbon monoxide and other well known toxic substances has resulted in a parallel reduction in the frequency of occurrence and in the severity of associated disease. Indeed, it has resulted in the elimination of occupational diseases specific to these agents over long periods of time when exposures have been maintained below the established tolerance levels.

Despite these successes, questions are being raised today concerning the procedures employed in developing dose-response relationships and the acceptability of criteria under which tolerance levels are derived. These questions relate particularly to two areas: (a) doubts are raised as to the long-term safety of any level of exposure which gives rise to a demonstrated biologic response of whatever kind or degree; (b) the possibility is emphasized that a poisonous agent, such as lead, quite apart from its specific toxicity, may contribute over a long period of exposure to the development and progression of one or another of the chronic diseases which commonly accompany aging. This may occur even though the exposure level was below the established tolerance limit.

1. Criteria for Establishing Tolerance Limits.

The first argument stems from the qualitative view of toxic reactions. A substance is recognized to have poisonous properties; therefore, its presence in any amount is potentially bad and any measurable response must constitute a warning against impending injury. This is in conflict with the quantitative view under which the tolerable level of exposure is established to keep the magnitude of a given kind of response within an acceptable limit. In such cases, the response is chosen because it is, indeed, a significant precursor of ill-health. Up to the permitted limit of the exposure, however, the response is not of a magnitude which will seriously disturb the organism. At the same time, those setting the limit recognize the variation in susceptibility to the agent among a group of individuals and they set the tolerable level of exposure low enough to safeguard the exposed population within an "acceptable" probability of occurrence of responses beyond the established limit.

2. Environmental Stress as a Contributor to Chronic Disease

The second point of criticism has to do with a different etiologic concept: that the agent acts only as a secondary factor, speeding up the onset or increasing the severity of chronic degenerative disease, the basic cause of which lies elsewhere, possibly within the individual himself. This is much more difficult to deal with than the causal relation between a toxic agent and a specific occupational disease. The claim is simply that there is an excess in the occurrence among the exposed groups of one or another of the chronic diseases seen regularly in the adult population. It is recognized that the probability of occurrence of these diseases varies widely among aging people for a variety of reasons other than occupation. To demonstrate that a unique excess of disease does exist, in fact, and is properly chargeable to the exposure situation, one must be sure the comparison is made with another population, equivalent in all respects except in the matter of exposure to the suspected agent.

The fact that these questions are unanswered justifies the institution of a major research program to provide a firmer foundation on which to derive tolerable levels of contact with hazardous environmental agents. The need is for investigation that will have meaning across broad classes of agents, grouped according to the nature of their action on man.

> ***Recommendation 3–1:*** **It is recommended that the National Institute of Environmental Health Sciences support a research program specifically designed to develop criteria for establishing safe limits of occupational exposure to hazardous environmental agents. This program should take into account the kind of biologic response in man which may be related to health impairment, the maximum degree of response of the stated kind which is to be accepted, and the probability of occurrence of responses up to the stated limit which is to be permitted in exposed populations.**

At the outset of this proposed program, the following are suggested as areas of interest:

a. New Research Tools

Systematic inquiry should be undertaken to evaluate present methods and to develop new ones in areas of physiology, biochemistry, psychology, etc., for the identification and assessment of impairments in man in response to environmental stresses and to distinguish these from the methods of medical examination which are intended to assess disease and disability. The usefulness of these measurements of impairment as early predictors of impending ill health must be validated by human studies involving real environmental exposures.

b. Basic Versus Applied Toxicologic Research

It is useful to distinguish between two kinds of dose-response relationships. One portrays the relation between the effective dose at the critical site within the body and the magnitude of the underlying biologic response resulting therefrom. The second type results from an epidemiologic study which shows how the degree of ill health experienced by exposed people varies with different levels of environmental exposure. There are a number of important events which operate in the environment and internally to determine the difference between the two portrayals of the dose-response relation. A program of research is needed to inquire systematically into the many and varied influences that mediate between the external level of exposure and the effective dose at the critical site and those concerned with the course of events between the basic disturbance and consequent loss of health.

c. Human Versus Animal Studies.

A better basis is needed to answer the question: What kind of response serves best as a predictor of ill health and at what level of response should the selected index be limited to insure a reasonable margin of safety? There is great need to supplement animal studies with epidemiologic studies on populations at risk in search for answers to these questions, especially in assessing the contributory role (as distinguished from primary action) of the agent in the development and progression of chronic disease.

E. Evaluation of Occupational Exposures

1. General Studies.

a. Studies of Work Environments.

One of the difficulties in developing a national program to control industrial exposures which adversely affect health and to improve the work environment has been the inability of national and state agencies to set goals and, more importantly, to measure progress toward attaining these goals. One might look at the problem of industrial health as one of monitoring and improving the work environment of the nearly 80 million people currently in the labor force. The work environment of these workers could be described by examining a random sample of the some 3 million places at which they are employed. The existence of a national social security system and state unemployment programs generates sampling frames from which a highly sophisticated selection of work places could be made so as to permit generalizations to all or segments of the employed population of the United States.

Viewed from the national level, a sample of work places could be selected from records maintained by the Social Security Administration and used by the U.S. Bureau of the Census for their annual publication, "County Business Patterns". These records are part of the established reporting system of the Social Security Administration and are the result of applications made by individual employers for identification numbers to be used on their Social Security tax returns. "County Business Patterns" (Bureau of Census, 1969) shows numbers of work places by county, by Standard Industrial Classification code, and by number of employees for the entire United States. It is possible, therefore, to identify sampling frames by area of a county, by type of industry, and by size of industry, and systematically to inspect a sample of these work places.

Some of the by-products of such a survey would be a more formal identification of those aspects of the work environment relevant to occupational health, the standardization of inspection procedures and the development of standards. In addition, a continuous series of statistical data would be available from which trends could be identified and progress toward goals measured.

Surveys of this nature have been recommended in the Frye Report (1966) and have been implemented by a number of local health departments. They have not, however, yet been carried out on a national level. Some of the techniques have been tested or are actually in operation by the Bureau of Labor

Statistics for the reporting of industrial accidents. For the most part, the technology is now available for the implementation of such a national environmental monitoring project.

Recommendation 3–2: It is recommended that a random sample of approximately 3,000 work places in the United States be studied each year. Such study would include inspection for the presence of potentially harmful materials or physical agents, a description of such things as lighting, health units, first aid facilities or arrangements, compensation awards, work absence levels, medical care arrangements, major psychologic stresses of the work and work environment, and a recommendation for each work place as to whether industrial hygiene service is needed.

b. Studies of Industrial Health Hazards.

It is not difficult to single out specific industries where environmental health hazards potentially exist. The chemical industry, automobile repair shops, dry cleaning establishments, and industries where considerable dust is generated are examples. A systematic scheme is needed for determining the actual extent of hazards in such industries.

Such a systematic plan could cover efficiently a large segment of the labor force within a given period, following an established set of criteria for the selection of each industry and using the latest statistical methods.

Using records maintained by the Social Security Administration, one can select and study samples of work places falling under any rubric of the Standard Industrial Classification. The content of each study would vary depending on the supposed nature of the environmental hazard, but in all instances should include environmental measurements and medical examination of the work force. In some instances, psychologic and physiologic examinations should be included. In many instances, workers would be followed for long periods of time. This would not only permit the detection of diseases with long latent periods but would also provide data on the selective process that led to the establishment of the initial cohorts.

Some elements of this proposal have already been carried out. Recent examples include studies of a randomly drawn selection of coal miners and uranium miners, with the latter including a long term follow-up to determine the incidence of lung cancer.

Recommendation 3–3: It is recommended that a comprehensive plan be developed and implemented for the study of industrially defined segments of the working population, and that a set of criteria be developed to enable the establishment of priorities. Such criteria should consider the magnitude of the work force, the extent and significance of the exposure, the possibilities for corrective action, and the potential contribution to knowledge. The studies themselves should deal with measures both of the work environment and of the health of the exposed workers. The latest statistical techniques from the fields of sampling,

experimental design, and Baysian theory should be specifically incorporated.

2. Specific Studies.

a. Respiratory Disease—Etiologic Role of Industrial Agents.

(1) Gaps in present knowledge.

The biochemical, pharmacologic and immunologic mechanisms which lead to lung damage by environmental agents are insufficiently known. This hampers effective control of exposure since this knowledge is necessary to establish minimal exposure levels which can be tolerated without demonstrable harm. Knowledge of the prevalence of industrial lung diseases, and of the prevalence of aggravation of preexisting lung disease by industrial exposures, is also grossly inadequate.

These gaps in our knowledge are to a large extent the consequence of: one, the non-existence of an effective, systematic, coordinated and basic-science-oriented national program on the causation, prevention, and treatment of lung disease; two, the non-existence of an effective, systematic, coordinated and basic-science-oriented national program in occupational health.

(2) National research program in industrial lung diseases.

The establishment of a national program for the continuing surveillance of industries where workers are at risk of developing occupational lung disease is urgently required. This program should, in the first instance, include the initiation of surveys on the prevalence of lung disease caused by asbestos dust, coal dust, cotton dust, beryllium and silica dust. Such surveys should include active as well as retired workers, and should include the use of all appropriate X-ray methods, pulmonary function tests, and biochemical and pathological studies. The design of these studies should include the use of sophisticated measurements; reliance on simple tests only is not sufficient. The acute and subacute responses to dust in industry require further study. There is a discrepancy, for example, between the well-documented acute effect of carbon dust on airway resistance and its disputed role in causing disabling lung disease after prolonged exposure. In the case of byssinosis, the acute pulmonary function response to dust is probably valid as a predictor of future development of irreversible lung damage.

The program should also include pilot studies on other occupationally induced lung diseases. Such studies could include investigations of irritant gases, cadmium oxide, toluene di-isocyanate, and farmer's lung.

Industrial hygiene support for this program is necessary to provide techniques for environmental monitoring, to keep track of technologic trends, and to provide contact with engineering control efforts.

Continuous surveillance of industrial populations will be necessary, with changing emphasis as dictated by changing circumstances. The present proposal concerns a continuing in-depth surveillance of particular industries known to be hazardous. The survey program proposed in Recommendation

3–3 could complement the survey outlined here in several ways, e.g., by helping to select work places for in-depth surveillance, and by helping to identify new or as yet unknown sources of hazards which may require in-depth surveillance for lung disease. The proposed program should include provisions for cooperative efforts with broader programs as well as with control agencies. Some of the activities recommended elsewhere in this chapter (Recommendation 3–7) could be incorporated in the investigation, particularly in cases of exposures where enzyme studies are relevant.

It is also essential for this program to keep close contact with basic research developments, and in particular with advances in pulmonary function methodology.

The activities of the program should be centered on U.S. working populations. However, studies in foreign working populations should not be excluded, since these may provide conditions or exposures highly relevant to U.S. conditions, and in some cases, more amenable to study. Specific examples are studies on single fiber asbestos exposures (Canada, Cyprus, Finland, South Africa), and on textile dust exposures (Spain).

Recommendation 3–4: **The establishment of a national program for the continuing surveillance of workers exposed to risks of lung disease in industry is urgently needed. This program should have solid basic science as well as industrial hygiene support, and should in the first instance address its activities toward the recognition, assessment and control of the lung diseases caused by asbestos, beryllium, coal dust, cotton dust, and silica dust.**

Recommendation 3–5: **The study of acute or subacute pulmonary function responses to dust in industry should receive more emphasis to determine which responses are valid predictors of irreversible lung disease.**

(3) Basic mechanisms

The need for the studies to be grouped under this heading arises from the gap identified earlier. There is an urgent need for work on the basic mechanisms which are involved in the causation of highly prevalent and disabling lung diseases such as asthma, chronic bronchitis and emphysema. In addition, work along similar lines is needed to clarify the mechanisms which lead to lung diseases caused by inhalation of dusts, aerosols, and gases in industry. Because both goals require quite similar research approaches, any attempt to discern, within this general area of endeavor, between what is environmentally related and what is not, will probably be found impossible. In particular, when basic mechanisms of disease (e.g., at the cellular level) are involved, a direct relationship between such mechanisms and environmental factors may not be obvious at the outset. For these reasons, the Subtask Force recommends that NIEHS strongly support these areas of study. Only through increased basic knowledge of the response patterns of the lungs and their physiologic consequences may we hope to bring, eventually, some order to the now confused field of the development of environmentally related lung disease.

The relative contributions of environmental factors on the one hand, and of genetic and other host factors on the other, are in many instances difficult to distinguish. This means that one will usually have to take a broad viewpoint in judging "environmental relevance" in this area of research. Insistence on close relevance to identifiable environmental factors will undoubtedly hamper progress in building up a basic body of knowledge. For instance, the environmental relevance of studies on physical properties of inhaled particles and their handling in the airways is obvious. Yet, detailed studies in this area may not contribute directly to knowledge of the response of the lungs to noxious particles; they merely describe a route of access. In contrast, basic studies on intracellular organelles and biochemical pathways in alveolar macrophage cells may seem to have no direct environmental relevance. Yet, such studies have already had an impact on our understanding of responses to environmental agents.

Similarly, studies on metabolic pathways in lung tissue, such as those involved in the production and breakdown of chemical mediators, may help to clarify response patterns at a basic level, and thus may yield information relevant to a wide spectrum of environmental agents. Similar remarks could be made for basic pharmacological and neuro-muscular studies on lungs and airways. Since most environmental agents (industrial as well as general air pollutants) have poorly defined pharmacologic characteristics, much can be learned from responses to better known pharmacologic agents.

There are indications that ventilatory lung function may start to deteriorate between the ages of 15 and 25 in males. It is now possible to distinguish between effects of growth on the one hand, and pathologic changes in lung function on the other, in children between the ages of 6 and 18. This should facilitate the study of early effects of environmental agents.

Techniques are now available to study most aspects of pulmonary function quantitatively, *in vivo,* in man and in experimental animals. Also, concepts and techniques from biochemistry, pharmacology, and immunology can be brought to bear on the problems of the pathogenesis of environmentally induced lung disease. The recommendations below illustrate some of the problems which remain to be solved.

Recommendation 3–6: **The following topics urgently require support:**

(i) Detailed studies of the alterations of mechanical and gas exchange conditions in the lungs which result from environmental exposures in industry or in the laboratory.

(ii) The nature of the fibrogenic response of lung tissue, as in silicosis and asbestosis.

(iii) The role of chemical mediators and the immune response of lung tissue.

(iv) The function of alveolar macrophage cells, their role under physiologic conditions and in lung disease.

(v) The mechanism of lung tissue destruction in emphysema.

(vi) The physiology and pathophysiology of mucous glands and goblet cells in airways.

(vii) The physiology and pathophysiology of airway smooth muscle.

(viii) The neural control of airways; its interaction with effects of environmental agents and endogenous mediatory substances.

(ix) The causes of individual differences in sensitivity to environmental agents and endogenous mediators.

(x) The physiology and pathophysiology of the mucociliary clearance mechanism.

(xi) Studies in the development, growth, and aging of lungs, in particular below the age of 30.

(4) Technologic requirements

The Subtask Force suggests that consideration be given to the design of automated pulmonary function procedures suitable for field studies. The use of small specialized computers would probably yield more rapid results than reliance on terminals linked to large computers. Accurate and reliable methods for recognition and determination of fibers and fibrous materials in lung tissue need to be developed.

b. Exposures to Specific Chemicals

(1) Individual susceptibility.

It has always been evident that individuals vary widely in susceptibility to injury from specific chemicals. The preface of the threshold limit value tables states that "nearly *all* workers may be repeatedly exposed . . . without adverse effect" (ACGIH, 1968). Some of the factors responsible for variability, such as the observation that the obese and the alcoholic are unusually susceptible to injury from chlorinated hydrocarbons, have been known in general terms for some time. The discovery of genetically mediated deficiency in glucose-6-phosphate dehydrogenase activity revealed a specific cause for high susceptibility to agents which produce hemolytic anemia. A simple clinical test will reveal deficiency of this enzyme. For this reason, determination of susceptibility before any exposure has taken place is now possible.

All systematically active chemicals are candidates for similar discoveries, because all act on the body through their effect upon enzymes, or are biotransformed by enzymes into substances of reduced or enhanced toxicity. Every new clinical test which will detect special susceptibility before exposure to a chemical in industry is a contribution to maintenance of occupational health. It seems probable that discoveries of decreased susceptibility are also likely, particularly to chemicals whose toxicity is increased by enzyme action, e.g., parathion and benzene. A worker less susceptible to a particular chemical can be assigned to jobs where exposure is hard to minimize.

Current biochemical research on inborn errors of metabolism is largely directed toward non-occupational diseases and defects. Occupational health would be more rapidly benefited by research directed toward enzymes important in connection with exposure to systemically toxic chemicals used in industry.

Recommendation 3–7:

(i) A literature survey should be undertaken to collect information on enzyme systems known to be active in the human in the biotransformations of systemically toxic atmospheric contaminants in industrial exposures;

(ii) A study on humans should be undertaken to identify such enzyme systems when none have been reported for particular contaminants;

(iii) Reliable clinical tests should be revised to make practical the assay of the activity of such enzyme systems in individual workmen;

(iv) Surveys should be conducted on the variability in activities of these enzyme systems within the working population.

The results of these investigations should be published to furnish a tool to occupational medicine by which workmen hypersensitive to particular contaminants may be detected and excluded from exposure and resistant workmen can be identified for safe exposure where limitation of airborne concentrations is impractical.

(2) Combined exposures

Studies to determine acceptable exposures to chemicals almost invariably concern one chemical at a time. However, it is difficult to find an occupational situation in which a workman is exposed to only one potentially injurious stress. Experience and limited experimental work suggest that a large proportion of possible mixtures of chemicals act additively upon the body, and the application of threshold limit values to mixed exposures (ACGIH, 1968) ordinarily assumes additive action.

The situation is less well understood in respect to combinations of a chemical exposure with a physical stress, with medication, with nutritional deficiency, with physiologic states such as pregnancy, immaturity or advanced age, or with acute illness.

Recommendation 3–8: **It is recommended that a systematic program be undertaken to study upon animals, later confirming with human subjects, the effects of exposure to industrial atmospheric contaminants, a) in combination with exposures to physical factors (such as high and low temperatures and humidities), b) in combination with medications commonly used by industrial workers, c) in combination with physiological states such as pregnancy, immaturity, advanced age, nutritional imbalances, and d) in combination with frank but not disabling illnesses.**

c. Trace Elements—Prevalence, Hazards and Modes of Action

(1) Deficiencies and toxic excesses of trace elements

Study of the prevalence, hazards, and modes of action of the trace elements are areas of research that have yielded, and will continue to yield, great benefits to man. The toxic or potentially toxic concentrations which characterize today's chemical pollution demand improvement in preventive measures. The elements essential to human health must be studied more, and better corrective therapies developed for deficiencies. Too much of some and too little of other elements are costly environmental health hazards which can be corrected.

Toxic concentrations of trace elements enter the biosphere from industrial wastes, smoke, automobile exhaust fumes, and other sources. Lead is a prime example of a trace element which has long been recognized as an occupational hazard, but in recent decades has assumed even greater concern because of other types of environmental exposure. Public health problems associated with clinical intoxication from occupational exposure have been largely replaced by accidental poisoning of non-occupational groups; even more importantly, there is reason to suspect a general increase in population exposure due to widespread pollution of the atmosphere through the use of leaded gasoline. Population surveys have shown a graded relationship between blood and urine levels of lead and the degree of human exposure to atmospheric lead. Because "natural" levels of lead in body tissues are not known, it is impossible to assess the margin of safety between observed levels and those known to have biologic effects.

In some instances, the best defense against toxic concentrations of a given trace element may be adequate amounts of one or more other essential trace elements. An example is the protective action of selenium and zinc against the toxic effects of cadmium, an element which causes sterility and produces hypertension in experimental animals.

Correction of essential element deficiencies in Western civilization has resulted in important gains in health. Fluoridated water, iodized salt, and iron therapy are trace element therapies that have greatly benefited man. Correction of other trace element deficiencies has resulted in substantial improvement in crop yields and has increased the feed efficiency and health of domestic animals. Evaluation and correction of excesses and deficiencies may similarly result in health benefits for man.

(2) Trace element profiles

Maintaining the proper elemental composition of the body is considered essential to good health. Important aspects of the internal environment of man can be studied easily today by analyses of whole blood, plasma, and serum. Profiles of the trace elements can be determined and related to regional and occupational variations in health and disease. Analytic methods are available for many elements, and automation of these methods is being developed.

Surveys of regional trace element profiles can be conducted in the United States, with the aid of the Red Cross Blood Bank collection centers. A prototype study of this sort has been carried out by the Eastman Dental Center, Rochester, New York and Cornell University, Ithaca, New York. Regional differences were disclosed in the blood contents of cadmium, copper, lead, molybdenum, selenium, and zinc. Special arrangements would have to be made for blood collection in industry. Profiles of the blood trace element patterns of patients with proven degenerative disease can be obtained by means of blood samples collected from various medical centers.

An example of the importance of trace elements is the effect of fluoride on dental health. Fluoride concentrations above 0.5 ppm in community drinking water correlate inversely with dental caries experience; lesser fluoride concentrations show no such consistency. Recent observations on man and on experimental animals suggest that several elements in the water or in the soil (thence in locally grown foodstuffs) may influence dental health. A decreased caries incidence may be associated with the presence of boron, strontium and molybdenum (perhaps with lithium and vanadium) at unusually high levels, and conversely an increased caries incidence with relative excesses of copper, manganese and selenium.

Recommendation 3–9: **A program should be developed to:**

(i) Undertake systematic blood analysis to determine regional occupational and degenerative disease profiles for the trace elements;

(ii) Develop automated methods for rapid and inexpensive analysis of trace elements in whole blood, plasma, and serum;

(iii) Correlate regional and occupational blood trace element profiles with incidence of occupational and degenerative diseases;

(iv) Support study of the modes of action of the trace elements in both man and animals. Study of the interrelations of the elements requires special emphasis.

F. *Perceptual and Mental Factors*

Service occupations show a steady increase with time; therefore the field of occupational health will increasingly tend to be centered on environmental problems of service occupations. Examples are occupations related to banking, insurance, transportation, retail trade, and federal and state government. Technological change is rapid in both the manufacturing and service sectors. The following quotation is taken from the report of a 1965 survey of some 40 industries by the U.S. Department of Labor (1966):

> "Prospective technological changes will continue to reduce the proportion of jobs involving primarily physical and manual ability to work with data and information . . . A few operators of mechanized handling equipment or conveyors can often do the work done by a number of manual materials handlers . . . Increasingly, the function of the factory operative is to patrol a number of automatic machines and to be responsive to signals indicating breakdown . . . In process industries, the typical operator will monitor a wide panel of control instruments and record information for interpretation . . . routine maintenance on new equipment is often reduced by means of devices for automatic lubrication of machinery . . . Electronic data processing (EDP) will reduce the relative proportion of routine office jobs, . . . but will require new and higher grade jobs to plan, program, and operate such systems."

Thus, the majority of workers will in the future occupy white-collar jobs with little exposure to the older types of environmental hazards such as toxic atmospheres, dangerous machinery, and noise. Environmental health hazards of future industry will derive from the perceptual and social environment of the worker and from the nature of the tasks performed. Full automation of manufacturing processes with truly unattended operation is not yet a reality except in isolated instances, and some degree of direct physical exposure to health hazard will be present in diminishing amounts for the foreseeable future.

1. Mental Load and Its Effects.

The health consequences of the changes sketched above will be to emphasize the relative significance of the worker's capacity to process information, his memory, and his power of rapid accurate decision, as against his muscular strength and dexterity. Industrial physicians will be increasingly concerned with ensuring integrity of these functions by monitoring the onset of strain due to mental overload.

The specific objectives of a study on mental load and its impact on health would be: to identify health relevant categories of mental load and stress; to establish maximum nonhealth-hazardous levels of mental load and maximum safe exposure periods where relevant; and to categorize individual variables, such as age, causing differences in susceptibility to overload.

The *independent variable* would be the nature and quantity of mental load imposed on workers by selected types of industrial and service task assignment, as measured by such currently available instruments as required sampling rate (monitoring tasks), information through-put (data-processing tasks), timespan of discretion (supervisory and managerial tasks). Task analysis would be required to identify components of workload. *Dependent variables* reflecting health status would be the ratio of medical to nonmedical complaints, sickness absence history, absenteeism, job turnover, use of self-medication and related indicators. There are grounds for believing that a significant fraction of reported sickness absence is in effect a response to mental overload. In effect, the worker appears to use permitted sickness-absence to take a needed rest to recover from the resulting strain.

Studies of this type have already been undertaken on a relatively unscientific basis in airline pilots and truck drivers. However, these cases are exceptional since they involve the safety of the public, and there are many others where the health and efficiency of the worker himself is of prime importance, and still others where within-plant accident-frequency could be an additional health hazard compounding the effects of overload.

In certain other cases, too low a mental load is believed to impair efficiency by reducing alertness and this situation may also, though less probably, have health consequences. The extreme case has been demonstrated in the laboratory in so-called perceptual-deprivation studies. A few such tasks are encountered in highly automated industry. However, the latter aspect of the proposed study is judged to have a low priority.

a. Safety Hazards Due to Mental Overload in Critical Tasks.

Within the general field discussed above, particular urgency should be assigned to studying the mental load of air traffic controllers, bus and truck drivers, commercial airline pilots, merchant marine officers, and others whose moment-to-moment decision-making capacity impinges directly on public safety.

Based on the tools and procedures outlined above, scientifically-based procedures should be developed for setting safety limits on task intensity and duration, for future use by regulatory agencies such as the Federal Aviation Administration and the Maritime Administration.

b. Perceptual and Mental Fatigue

The phenomenon of mental fatigue may be defined as performance decrement due to high mental load. It is distinguished from the cognate phenomenon of boredom by short-term irreversibility. Mental fatigue is a subjectively common, indeed universal, phenomenon of general concern in industry. As indicated above, its occurrence is believed to be associated with non-specific illness.

While important, the concept has proved difficult to test. Further basic research is needed but sound guidelines are not easily established. Patterns of performance decrement and the differential effects of certain drugs and environmental stressors, such as heat, suggest that a distinction should be drawn between at least three components. The first is short-term loss of perceptual discrimination. This is found in forced-pace inspection and other fast detailed work such as stitching. The second is medium-term memory overload. This causes errors in data-transmission tasks, omission of required behavior, etc. The third is longer-term impairment of high-level skills. This appears to be associated with frequent making of difficult decisions and impairs capacity for judgment.

These phenomena can all be tentatively explained in terms of what may be called "neural noise" affecting different functions and with differing decay time constants, from seconds through days.

Further field and experimental studies appear to be required to establish the separate effects which together comprise mental fatigue. The results would be of direct value in studying the health impact of the industrial environment, and in setting guidelines for rest and recreation periods.

***Recommendation 3–10:* It is recommended that a program of behavioral studies be initiated to analyze:**

(i) The health impact of differing levels and types of data processing, decision-making, and supervisory workload through field studies on the short- and long-term health and efficiency of selected groups of workers;

(ii) Public safety hazards due to paced performance of critical decision-making tasks;

(iii) The nature and health consequences of preceptual and mental fatigue in industry.

2. Assessment of Environmental Stressors by Behavioral Methods.

A number of environmental stress conditions such as noise, heat, atmospheric contaminants such as carbon monoxide, hyperbaric oxygen, and drugs such as alcohol, nicotine, and tranquilizers, are known or believed to exert behavioral effects mediated by the central nervous system when experienced in concentrations much lower than those currently recognized as physiologically safe. Some functions affected are perception, short-term memory, vigilance, skill acquisition and retention, time and space orientations, and motor control. Some agents such as CO are also known to produce behavior and performance deficits capable of causing accidents. Other agents, though they do not produce directly detectable effects on normal task performance, are believed to reduce the margin of safety by loading an operator's data-processing and/or memory capacity to the point where minor task overloads cause catastrophic breakdown. Still others cause narrowing of attention (so-called "tunnel vision") and introduce safety hazards due to failure to respond to critical signals. Sensitive behavioral tests are required to detect and measure the low-level behavioral effects.

A limited number of psychomotor tests have already been devised and used in field studies to measure performance decrements due to various stressors. However, no standard battery is available on a routine operational basis for assaying the behavioral effects of stressors and research should be directed toward development and standardization of such a test package.

The research envisaged would draw primarily on experimental psychology, psychometry, and statistics, as well as medical and pharmacologic knowledge of drug and other stressor effects.

> ***Recommendation 3–11:*** **It is recommended that studies be undertaken to develop behavioral methods for determining the effects of drugs, toxic agents, and environmental stress such as heat and noise on mental functions and behavior.**

3. *The Skill Factor in Accident Prevention.*

Traumatic accidents continue to be a major hazard both in industrial and general community exposure. There are inherent limitations on the effectiveness of environmental and task-centered countermeasures such as equipment design (e.g., of production plant and domestic equipment), due to the need to maintain adequate system performance; hence it is only rarely possible to eliminate all risk by safety engineering and design changes. Generalized safety propaganda has been shown to have transient and limited effect.

In certain cases industrial accident-rates have been shown to decrease dramatically during a period of exposure to a specific plant or job, skill and experience being apparently the main preventive factors. In the present context the term "skill" is interpreted broadly to include well-organized perception, direction of attention and local decision-making, as well as simple manual dexterity. Thus, there is evidence to suggest that skill-deficit is a major factor in accident causation and research should be directed toward better understanding and exploitation of this factor.

> ***Recommendation 3–12:*** **Emphasis should be given to research to investigate the role of skill and experience in preventing industrial and**

community accidents. The possible role of improved product and equipment design in facilitating the acquisition of skill, and hence, in contributing to safety, should also be studied.

II. Hazards of Consumer Products

A. The Problem

The mission of the NIEHS in community health is broad. As practical limitations on this mission are defined, the Subtask Force recommends that a portion of this effort be focused on considerations of the health and safety hazards of consumer products. At first glance, this may appear to be a rather limited problem. However, when one considers the variety of hazards which can and do arise from the spectrum of product types with their almost incomprehensible and lengthy list of ingredients, used and misused in unpredictable ways by a heterogeneous population, the task assumes mammoth dimensions. The recognition and control of every aspect of the health and safety of consumer product hazards seems to be practically impossible. The limited objective of seeking those hazards which should be the responsibility of the NIEHS constitutes a sufficiently difficult task.

It is incontestable that the safety of consumer products is important and that additional research on safety is needed. But these axioms are not helpful; the truth of the matter is that an analysis of the problem cannot be made at this time. The facts of consumer injuries (e.g., the categories of products involved in serious injuries) are not known. In the discussion to follow, these needs will be presented in an abbreviated description of the present status of the problem and of certain future research goals. This will include an evaluation of injuries from consumer products as compared to the national picture of accidental injury.

Accidents are the number one cause of death from ages 1 through 37. In each of the three years, 1964–1967, an average of fifty million persons were injured accidentally. Eleven million were disabled to the point that bed care was necessary and 112,000 were killed. Accidents involving motor vehicles are disproportionately lethal, causing about half of all accidental deaths. Nearly 28,000 deaths followed home accidents; of these about 18,000 involved consumer products. A comprehensive study destined to reveal "the identity of categories of household products . . . which may present an unreasonable hazard to the health and safety of the consuming public" is the mission of the newly established National Commission on Product Safety (Senate Joint Resolution 33, 1967).

The acute toxicity of products and their potential for traumatic injury are of lesser concern to the NIEHS than the deleterious effects of long-term, low-level exposures. Categories of products not under consideration by the National Commission on Product Safety (NCPS) should therefore be reviewed by the NIEHS.

The total of annual injuries from toxic products is estimated to be about 1.6 million. This total is much greater than might be imagined from the 3,000 deaths listed (CPEHS, 1968). The estimate or the 1.6 million total includes 25,000 injured from toxic hazards of recreational equipment, 130,000 from flammable liquids other than from burns, 540,000 from laundering and cleaning products and 75,000 from pesticides.

B. Research Needs and Recommendations

Most of the current efforts to control accidents employ primitive methodology. More sophisticated research is needed and it should follow two general lines: 1) A systematic, descriptive approach delineating the patterns and seemingly chance events (this would supply knowledge of the frequency and distribution of accidents); and 2) an analytical procedure identifying the factors causally associated with accidents.

The health and safety hazards of consumer products have not been neglected in the past. Various responsibilities have been assigned under the Food, Drug, and Cosmetic Act (1968), under the Hazardous Substances Act (1960), under the Flammable Fabrics Act (1953), under the Federal Firearms Act, and under other legislation. The National Commission on Product Safety has currently listed 23 categories of products that will hold its attention (Elkind, 1968). Many of these include products with toxic hazards.

The task of identifying the urgently needed studies of the health hazards of consumer products can be made somewhat easier by excluding those fields not readily demonstrated to lie in the province of the NIEHS. Removing the multiplicity of problems clustered about traumatic injury deletes most of the consumer product categories listed by the NCPS, such as power lawnmowers and wringers on washing machines. Peripheral positions have been assigned to injuries from drugs (for example, allergies), from military agents (such as tear gas), from serious cultural problems (such as drug abuse and addiction), and from radiological hazards except those not covered by other specific legislative assignment.

Any research effort undertaken in this area should have a possibility of bringing some order into the veritable sea of product hazards. One such approach is found in an epidemiologic framework since the toxic hazards of consumer products are related to the interaction of three important variables: the nature of the product, the consumer, and the environment.

As emphasized by Johnson (1968), there remains "a continuing need for more extensive reliable data as the basis for a meaningful assessment of the problem." Among the most important of these data are the categories of household products involved in toxic injuries. The heavy toll of lives blighted or lost makes the need to discover the serious offenders an urgent one.

***Recommendation 3-13:* The categories of products frequently involved in toxic injuries should be identified.**

Two existing systems of governmental reporting could with "almost no additional expense" (Dickerson, 1968) collect the basic data. These are the National Health Survey and the Poison Control Center—National Clearing House Network (Gleason, 1965). A third—a hospital-based system established by the

Office of Product Safety of the Food and Drug Administration in cooperation with the Environmental Control Administration—has just been authorized and will soon be operational. Data from this system, which will be computerized, will include facts on injuries to patients reporting to emergency divisions of hospitals. Data will be collected from 62 hospitals and will include the nature of the agent causing the injury plus other details. This project represents a promising beginning and should be expanded to a national scale.

The sheer weight of numbers forces a discrimination among household products on the basis of the seriousness of the injury threatened. The NIEHS should focus its attention initially on the chronic toxic effects of household products presenting unreasonable hazards with significant threat of serious toxic injury.

At present the consumer who realizes that he has in his home a hazardous product has no place to turn except perhaps to call the local police or fire department, to write to the Food and Drug Administration, or to approach the manufacturer with his complaint. An "ombudsman" named in each city or region to receive such complaints (Gleason, 1969) would serve two important roles: unreasonable hazards would be exposed and removed; unfounded nuisance claims would be unprofitable since liability payments would be made only on the basis of substantial demonstrations of cause and of injury. The ombudsman would send information routinely to state and federal clearing houses and thus serve as an effective reporting source. Furthermore, genuine unreasonable hazards would be discovered, hopefully before injuries occurred.

Relevant information on product safety should be available to the consumer as well as " to those in the most strategic positions to protect the consumer" (Dickerson, p. 87, 1968). Thirty-three departments and agencies of the Federal Government acknowledged in 1961 that they conduct some type of consumer protection activity. A sizable list of private organizations aid consumers (e.g., American Home Economics Association, American National Standards Institute, Consumers Union, Good Housekeeping, National Safety Council, and Underwriters Laboratory). The General Services Administration with its trained personnel and equipment carries out a major testing program for federal purchases. The findings of these tests are not made public. "Access to the GSA findings would be helpful to any investigation of product safety." (Dickerson, p. 87, 1968)

C. Safety Standards

When a federal agency receives by legislative action the responsibility for protecting the public health by controlling certain hazardous or potentially hazardous substances, regulations are promulgated by the agency establishing standards which govern such products. The standards are based on evaluations drawn from the results of scientific research and from other factors which enter into a judgment of the relative benefit-to-risk balance. Developing the standards is a difficult, demanding task requiring an appreciation of the consumer-product interaction, knowledge of the effects of the product on health, the state of the art for the class of products, and the economic factors involved, e.g., the loss of time and the relative seriousness of the injury.

Under the Hazardous Substances Act, standards for acute toxicity, flammability, irritancy and other hazards have been in use for several years. For most of the host of products covered by this Act, the hazards (if any) of chronic exposures are virtually unknown. For example, how should the health hazards from the daily use in a single household of an aerosol-propelled pesticide, a deodorant, and a cosmetic hair spray be evaluated? Time to accumulate human experience cannot be allowed.

> ***Recommendation 3–14:*** **Research is needed to define criteria on which safety standards should be based.**

III. Summary

The establishment of a tolerable level of exposure to a hazardous physical or chemical agent, below which man is capable of dealing with the imposed stress without significant health risk, is a fundamental need in the design and operation of practical control programs against environmental health hazards. For the occupational problems of the future, the Subtask Force recommends that attention be increasingly focused on chronic injury or disease arising from single or multiple potentially toxic exposures. Tolerance levels for exposure should be set, not agent by agent, but by evidence of derangements in physiologic or biochemical functions of the body (Recommendation 3–1).

The Subtask Force also suggests the establishment of a program for a systematic and on-going random annual sampling of 3,000 of the 3 million work places in the United States. This will permit the identification of those aspects of the work environment relevant to health, provide a basis for inspection standards as well as for standards of environmental conditions, and permit state and national goals of control to be described (Recommendation 3–2). In addition, over the next score or more years, a systematic investigation of the hazards of the work environment should be made based on measurements in the environment together with health examinations of the exposed workers. The selection of industries ultimately should include a large segment of the labor force (Recommendation 3–3).

As a part of this overall program, workmen in industries with high risk of lung disease should be regularly examined. Changes in pulmonary function in response to acute exposures may predict the ultimate development of chronic disease. It is believed that basic studies of pulmonary physiology and pathophysiology can eventually bring order into the confused field of occupational lung disease (Recommendations 3–4 and 3–5). Additional topics which were identified by the Subtask Forces as urgently requiring support include the following (Recommendation 3–6):

1. Alterations in the mechanical and gas exchange functions of the lung brought about by environmental exposures, including the basis of individual differences in response.

2. The nature of the fibrogenic response in silicosis, in asbestosis, and pneumoconiosis in coalworkers.
3. The function of alveolar macrophage cells, of mucous glands, of goblet cells in airways, and of the mucociliary clearance mechanisms.
4. The physiology and pathophysiology of smooth muscle, of neural control, of chemical mediators and of the immune response of lung tissue.
5. The mechanism of lung destruction in emphysema.
6. The development, growth and aging of the lungs.

The Subtask Force also recommended that enzyme systems be sought which will reveal the effects of exposures to toxic chemicals. These systems may serve to predict the degree of sensitivity of an individual before exposure (Recommendation 3–7). Another recommendation was that the effects of exposures to atmospheric contaminants with concomitant stresses from physical factors, medications, altered physiological states, and intercurrent illnesses be systematically explored, first in experimental animals and later in man (Recommendation 3–8).

Correction of trace element deficiencies have in the past been important to man's health and promise further gains. New analytical methods, when automated, will permit blood trace element profiles of a selected group of elements to be obtained quickly and relatively inexpensively. Regional norms, occupational and degenerative diseases may have characteristic profiles of diagnostic value. The Subtask Force urges that the modes of action of the elements and their inter-relations be studied (Recommendation 3–9).

As automation and mechanization increase, the occupational hazards from toxic exposures and machinery lessen, whereas those from decision-making and data-processing increase. It is the belief of the Subtask Force that field studies of the short- and long-term health and efficiency of selected groups of industrial and service workers will help to gauge the importance of these factors. Paced decision-making, if it distorts the judgment of key persons (air traffic controllers, bus drivers), endangers the public safety. Safety limits should be established based on scientific tests. Perceptual and mental fatigue as well as performance decrements from environmental stresses (carbon monoxide, alcohol, noise, heat) need evaluating. The problems are clear; the techniques to provide answers require further development. Skill and experience in certain industrial accident studies emerge as preventive factors in reducing accident rates. The Subtask Force recommends that this possibility be explored and correlated with investigations of the role of improved product design in the acquisition of skill (Recommendations 3–10, 3–11, and 3–12).

The evaluation of the toxic hazards of consumer products stands out as a pressing public health need. The first step, the identification of the categories of products involved in toxic injuries, should immediately be attempted (Recommendation 3–13). The new hospital-based program of the Food and Drug Administration and the Environmental Control Administration is a promising beginning which should be developed on a national scale. Steps which the Subtask Force believes are necessary to solve the health problems associated with consumer products include the following:

1. Standards for the control of the chronic toxic effects of household products presenting unreasonable hazards with significant threat of toxic injury should be provided;
2. An ombudsman for hazardous consumer products should be installed in each locality.
3. Relevant information on product safety should be made available.

The Subtask Force closed by citing the need for the development of criteria for setting standards of safety for the continuing use of household products. Chronic exposures to low levels of mixtures of materials pose difficult questions of hazard and much work is needed in this area (Recommendation 3–14).

BACKGROUND DOCUMENTS

Document Number	*Author*	*Title*
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CI–2	Hatch, T.	Concepts of Theshold Limits; Present Applications and Future Needs.
CI–3	Strain, W. H.	Prevalence, Hazards, and Mode of Action of Trace Elements.
CI–4	Bouhuys, A.	Respiratory Disease: Etiologic Role of Industrial Agents.
CI–5	Crossman, E. R. F.	Health Consequences of Industrial Environments on Perception, Decision-Making and Fatigue.
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CI–7	Smyth, H. F.	Some Research Needed on Systemically Toxic Atmospheric Contaminants in Industrial Exposures.
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Chapter 4

PHYSICAL FACTORS IN THE ENVIRONMENT, INCLUDING LIVING SPACE

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PHYSICAL FACTORS IN THE ENVIRONMENT, INCLUDING LIVING SPACE*

I. Introduction

Much of the history of man has involved an unceasing endeavor to gain control of the physical environment. In spite of many successes, the physical environment continues to play a dominant role in man's life, and new physical factors, brought into being by his inventive power, confront modern man with even more serious threats than cold and darkness presented to primitive man. These man-made or man-intensified physical factors include ionizing radiation, radio and microwaves, the coherent and high power light beams of lasers, infrared and ultraviolet radiation sources, machine generated noise, thermal stresses, vibration, and the crowding of living space.

A. Major Characteristics of Physical Factors

In an environmental health context, factors such as these tend to share some or all of four major characteristics:

1. They generally bear a close relation to energy use: thermal energy in the generation of power, electromagnetic energy in microwave devices and lasers, or acoustic energy in noise. Since per capita energy consumption is increasing concomitantly with the population and standard of living, the health hazards presented by physical factors will undoubtedly also be increasing steadily.
2. They are "field" factors in the sense that they confront the body of man with a disturbance conveyed by a spatially distributed field, such as acoustic, electromagnetic, thermal or gravitational fields. Their field nature implies an all-pervasive action, from which the individual usually cannot remove himself by a voluntary act.
3. They are frequently difficult to detect by human sensory mechanisms, as they are either physical phenomena operating in a range beyond the response characteristics of physiologic sensors, or they are factors, like crowding, the primary impact of which is often of a socio-psychologic nature. Their detection by instrumentation is also frequently difficult

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* This chapter was prepared by a Subtask Force chaired by Dr. Edward P. Radford, with Dr. James D. Hardy serving as Co-Chairman. Others who participated in its preparation included Drs. George Bugliarello, Alexander Cohen, William T. Ham, Jr., Robert J. Hasterlik, and Demitri B. Shimkin.

without trained operators and sophisticated devices, as in the case of psychologic effects.

4. In several cases, recognition or acceptance of the hazard is relative, conditioned by socio-cultural values. For example, crowding may be defined in different terms by different groups, and individual variations in noise or thermal sensitivity may have important socio-cultural bases.

Thus, although technologic developments are generally designed to benefit man, they frequently lead to or are accompanied by problems of an environmental health nature. It is incumbent upon public health authorities to be aware and capable of assessing and controlling these risks. As shown by the above discussion, however, difficult value judgments may be required in establishing sound criteria upon which the necessary control programs are based.

As a group, physical factors constitute potential hazards of major importance. Table 1 summarizes certain aspects of these factors in the environment, most of which are considered in greater detail in this chapter.

B. Organization and Training Needs

Certain special features stand out with respect to study of the physical environment at this time. Organizationally, research responsibilities in these subject areas show even more marked dispersion of responsibility than is found elsewhere in the field of environmental health sciences. One reason for this is that physical and engineering techniques, not generally understood by health professionals, are of major importance in the field. Another reason is that the health implications of particular physical factors have often lagged behind development of sources of exposure. For example, the study of heat and humidity has been a concern of physiologists interested in investigating basic mechanisms of response and is also the province of heating and ventilating engineers with little biologic background. Noise has not been considered an important hazard except for occupational exposures, and thus has become the concern chiefly of acoustic or industrial engineers. Finally, the health aspects of living space have been considered only in terms of architectural design. The common theme is that the health professions have been ill-equipped to study these subjects and that responsibility for understanding their effects on man has been assumed by other professions whose objectives often have little relationship to health.

Training for research careers dealing with the physical factors in the environment probably would be assisted by a more comprehensive view of these factors. For example, training in radiation effects could include all parts of the electromagnetic spectrum, and not be restricted to ionizing radiation as is often the case. Students being trained to study the effects of physical space limitations should also have an understanding of the effects of heat, cold and noise. It is the conclusion of the Subtask Force that some unification of training in the physical factors in the environment could be a useful result of this report.

TABLE 1. Summary of Environmental Health Aspects of Physical Factors.

Physical Factor	Origins of Exposure	Population at Risk	Potential Health Implications Particularly from Low Doses	Anticipated Ease of Control of Hazard
Ionizing radiation (high energy particles and electromagnetic radiation).	Natural sources; medical diagnosis and treatment; environmental release of nuclides; laboratory and industrial uses.	Whole population; special occupational groups.	Genetic change, cancer, life-shortening or "premature aging."	Difficult to avoid release of some nuclides into environment. Medical exposures can be reduced.
Ultraviolet radiation.	Sun, UV lamps, welders' arcs, etc.	Whole population for sun; otherwise small groups.	Skin cancer, senile changes in skin, eye burns.	Relatively easy to avoid exposure.
Lasers.	Occupational sources, surveying, communications, medical applications.	Small groups in special situations.	Retinal burns, skin burns.	Relatively easy, especially for eye exposures.
Infrared radiation and environmental heat and humidity.	Occupational sources, summer heat, winter cold; heat lamps, power generating stations.	Whole population. Small occupational groups.	Death due to thermal stress in sensitive individuals. Possible long-term effects of acute heat stress on thermo-regulation. Eye burns (infrared). Cold exposure important in elderly.	Difficult in view of number of sources and problems of heat dissipation. Cost may be a serious consideration in climate control of low cost housing.
Microwaves and radio frequencies.	Radar and other communications; ovens; industrial, medical and military uses.	Includes substantial proportion of the population.	Thermal effects at high energy. Non-thermal effects: cardiovascular and psychologic changes. Genetic effects reported.	Difficult in view of increasingly wide-spread use and problem of shielding.

TABLE 1. Summary of Environmental Health Aspects of Physical Factors. (Cont.)

Physical Factor	Origins of Exposure	Population at Risk	Potential Health Implications Particularly from Low Doses	Anticipated Ease of Control of Hazard
Noise.	Occupational sources, community and home sources, airports.	Special occupational groups, urban populations in particular.	Hearing loss, psychologic reactions, and non-aural effects on cardiovascular system. Startle reactions, loss of sleep.	Difficult for community noise sources. Supersonic jets may be serious problem.
Vibration.	Occupational sources, vehicular travel.	Construction workers, truck drivers.	Peripheral vascular disease. Neuromuscular effects. Visceral lesions.	Relatively difficult for certain sources.
Low and high barometric pressure.	Altitudes over 4000 ft. Underwater operations.	Large populations at higher altitudes. SCUBA and deep sea divers and special groups.	Low pressure: hypoxia, congenital malformations, synergism with other environmental factors. High pressure: bends, oxygen toxicity, nitrogen narcosis.	Low pressure: no control possible with altitude. High pressure: special undersea housing possible.
Physical space (congestion, crowding, and isolation).	Inadequate housing and planning of living facilities.	At least 10,000,000 people in substandard conditions. Special groups.	Abnormalities of childhood development, aggressive behavior, increased deterioration in the aged.	Difficult in view of failure to establish adequate criteria and to provide adequate new housing.

II. Ionizing Radiation

Since the potentialities for splitting the atom and producing multi-megacurie amounts of fission products became apparent, health effects of ionizing radiation have assumed considerable importance. In this field, a much greater awareness of subtleties of biologic damage developed than had previously been the case with other environmental agents. For example, for the first time, genetic considerations became factors in the setting of permissible exposure levels for an environmental hazard.

Sources of radiation exposures include natural background, use of x-rays and radionuclides in medical diagnosis and therapy, industrial and research applications of radionuclides and radiation producing devices, exposure of workers to radon and its daughter products in underground mining (particularly in uranium mines), and exposures of the general population through environmental releases of radionuclides from nuclear reactors and nuclear fuel reprocessing plants. Concurrent with the development of nuclear energy, standards or "permissible levels" have been recommended for external exposure to ionizing radiation and for the total body content of radioactive materials. Standards recommended by the National Committee on Radiation Protection* (NCRP), 1954 and 1959) were promulgated and enforced by the United States Atomic Energy Commission (Federal Register). Other "guides" for the control of radiation exposures of workers and the general population have been issued in recent years by the Federal Radiation Council (FRC, 1960, 1963, and 1967).

Currently, the suggested guides for whole body (gonadal) exposures, exclusive of natural background radiation or radiation given patients for medical diagnosis or treatment, are 500 millirems per year for individuals in the general public, and 5000 millirems per year for radiation workers. For exposures of the population as a whole, the recommended guide is 5 rems per 30 years. The guide for population exposure is slightly greater than that received from sources of natural origin. All such guides have been established on the assumption that the dose-effect relationship is linear and that there exists no threshold below which damage does not occur. As a result, the recommended guides represent a value judgment of the risk versus benefit of a given exposure. A very important issue is whether the recommended guides are properly established so that the risks associated with potential future increases in exposures can be properly evaluated and are, indeed, acceptable.

The areas of biomedical research discussed in this section are aimed specifically at resolving the question of how serious a small increase in radiation exposure to the whole population may prove to be as a health hazard.

A. Mechanisms of Action of Ionizing Radiation at the Molecular and Cellular Levels

Fundamentally, an evaluation of radiation exposure, as with other environmental agents, depends upon comprehension of the basic mechanisms of its actions at the cellular level. Of particular importance are the occurrence and basic nature of intracellular recovery and repair processes. Obviously, elucidation of the mechanisms of action of ionizing radiation in aqueous solutions and under defined physiologic conditions at the molecular and cellular levels will not answer all questions concerning effects on the total body. On the other hand, such knowledge will be of great importance for understanding and predicting dose-response relationships, as well as for the development of radioprotective agents which, for example, might act by enhancing normal cellular repair processes.

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* Now the National Council on Radiation Protection and Measurements.

Recommendation 4–1: **Basic research on the mechanisms of radiation effects at the molecular and cellular level should be given high priority support.**

B. Linearity and Threshold in Radiation Dose-Response Relationships

To date, human epidemiologic studies have not provided enough data to give adequate answers to the problems of delineating dose-response relationships and determining the existence of a "threshold" dose. More man-years of experience from these and other studies must be acquired. For better utilization of such data, consideration should be given to the establishment of a national depository for epidemiologic data and pertinent animal data dealing with the problem of dose-response relationships.

Because of prohibitive costs, the approach of exposing increasingly larger groups of animals has mitigated against large scale long-term studies. New approaches, including the use of more sensitive indices of radiation effects for both human and animal studies, must be developed. Lacking these, long-term studies using large numbers of animals remain the only approach available at this time.

Recommendation 4–2: **Epidemiologic studies of the effects of ionizing radiations should be continued and a national depository for pertinent information should be established.**

C. Hereditary Effects

The environmental health sciences have an important stake in the elucidation of the relationship of radiation dose to heritable genetic effects (WHO, 1957 and 1959). The influence of the dose rate on genetic changes needs further investigation. Also to be considered are the effects of gonadal exposures from long-lived radionuclides ingested at young ages or absorbed by the [illegible] *in utero*, particularly as these relate to genetic effects which may arise from general environmental contamination. Consideration should be given to techniques such as automated chromosome analysis for assessing the incidence of chromosomal anomalies in large population groups.

Recommendation 4–3: **Further research is needed to define and quantify the genetic effects of low-level radiation exposures.**

D. Carcinogenesis

A continuing effort should be devoted to the collection of data from human beings previously exposed to significant doses of radiation, as in the case of uranium miners, or people who at one time may have had a significant body burden of radioelements (Hasterlik, *et al.*, 1964). Studies of this type may yield further evidence on dose-effect relationships.

The end results of late radiation effects, e.g., tumor induction, shortening of life span, etc., are not specific for this environmental hazard. The interrelationships between chemical carcinogens or viruses and ionizing radiation in tumor induction are at present poorly understood. If the insult from combinations of these noxious agents is synergistic and not merely additive, these factors must be included in the setting of radiation guidelines and the planning of control programs.

Recommendation 4–4: **Research on ionizing radiation as a carcinogenic agent should be continued with particular emphasis on its interactions with chemical and viral agents. Epidemiologic study of cancer incidence in special populations exposed to small increases in radiation is also needed.**

E. *Acute Radiation Injury and Residual Injury*

Further studies of recovery from acute radiation injury should be conducted with a clearly designed program for testing the influence of total dose, dose rate and dose fractionation (Proceedings, 1968). The need to elucidate patterns of "residual injury" concerned with life span shortening, reduction in subsequent LD_{50} dose, oncogenesis, work capacity, and susceptibility to infections is indicated.

Increased emphasis is needed on studies of the fundamental nature of the "aging" process before its interrelationships with ionizing radiation can be determined (Atomic Energy Commission, 1963).

Recommendation 4–5: **Increased support should be provided for research on residual damage from single or repetitive radiation exposures to small doses. In particular, knowledge of radiation repair processes and the fundamental nature of aging is needed.**

F. *Effects of Highly Active Point Sources*

Because of difficulties related to the specification of "radiation dose" and "significant volumes" of tissue surrounding intense point sources (for example, ingested or inhaled alpha-emitting particles), the relationship of radiation dose to oncogenic effect is confounded (Dean and Langham, 1969). Moreover, the role of antecedent local tissue injury and cell death in tumor induction by point sources is poorly understood. These questions have important ramifications in the setting of radiation guidelines in certain industrial processes where the hazard consists of exposure from small, intensely radioactive particles. The number of people involved in these hazards at present is small, but a moderate level of research effort on this problem should be maintained. This is particularly important in relation to occupational exposure to inhaled airborne radioactive particulates with a size distribution of one micron or less in diameter, such as is the case with radon decay products in uranium mining

(NAS-NRC, 1961). An analogous problem is that of tritium which may be considered to act as a point source in molecules of biological significance such as DNA.

> ***Recommendation 4–6:*** **Basic research on the dosimetry (including microdosimetry) and tissue effects of intense localized sources of radiation should be given long-term support.**

III. Microwaves

The magnitude and extent of pollution of our environment by microwave radiation has not been systematically evaluated. The widespread use of microwave generators for military applications, radio-navigation, diathermy, communications, food ovens and for other industrial purposes has reached such an extent that one might conservatively estimate that nearly one-half of our population lives in a measurable microwave environment. Increased urbanization will move greater numbers into an energy field which did not exist one hundred years ago.

In view of the potential magnitude of this form of environmental pollution, it is reasonable to expect health authorities to have information upon which health and safety standards could be based. For the most part, such information does not exist. In the United States and Western European countries, there has been a willingness to accept the thermal hazards associated with microwave exposure, but little regard has been given to other effects. Opacification of the lens of the eye has been shown to occur at 100 milliwatts/cm^2. A level of 10 mW/cm^2 is currently used in the U.S. by the military and various industries as the maximum continuous occupational exposure. These exposure recommendations are the same for all frequencies. There are no specific exposure level recommendations for the general population in the U.S.*

Comparison of the preceding recommendation with exposure standards which are used in the Soviet Union and other Eastern European countries reveals a number of differences which warrant resolution. These countries, using non-thermal biologic effects as the basis for their standards, recommend as an exposure guide a level 1/1000 of that accepted in the United States. These non-thermal effects have been reported as central nervous system disorders, cardiovascular changes and other physiologic or psychologic effects which may or may not be transient. In addition, there is a tentative suggestion that mongolism may arise more frequently in offspring whose fathers were radar operators.

Differences in the exposure standards between the United States and the Soviet Union emphasize the need to support a research effort to provide the data necessary either to accept or to reject the non-thermal response concepts. Until the passage of Public Law 90–602, the "Radiation Control for Health and Safety Act of 1968", there was no designated federal agency assigned the responsibility to establish standards for microwave exposure. In contrast, Russian standards have been in effect for over ten years. Russian interest and research on both thermal and non-thermal effects have a long history and are currently very active (Dodge and Cassel, 1966). No comparable effort is underway in the U.S.

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*Subsequent to the writing of this Chapter, the Bureau of Radiological Health, U. S. Department of Health, Education, and Welfare, proposed a performance standard for microwave ovens of 1 mW/cm^2 for new units prior to sale and a limit of 5 mW/cm^2 thereafter (Federal Register, Vol. 35, No. 100, May 22, 1970).

A. Epidemiologic and Clinical Investigations of Microwave Effects on Man

Data are needed to determine the validity of the clinical and laboratory changes reported in the Russian literature. Studies of microwave workers and individuals treated with microwaves, along with appropriate control groups, should include a thorough analysis of the microwave exposure environment, including average power density, peak power density, frequency, and pulse repetition rate.

Recommendation 4–7: **Epidemiologic and clinical investigations should be undertaken of groups of workers or others exposed to high and low energy fluxes of microwaves. In particular, behavioral or physiologic effects should be investigated especially as they may be related to functions of the central nervous system or to congenitally derived disorders.**

B. Experimental Study of Microwave Effects

The current scientific literature includes reports of adverse biologic effects of microwaves at density levels below 10 mW/cm^2. More work needs to be done at low energy densities and particularly at different frequencies. The latter must include both pulsed and continuous exposures. Considerable effort should be directed toward investigating the cumulative effects of microwave radiation.

Animal experimentation similar to that performed in Eastern European countries should be started. Particular emphasis should be placed on central nervous system effects, conditioned response and reaction time changes. Spatial, electronic and dosimetric factors should be given special consideration. Additional effort on developing adequate energy density measuring instruments will be required.

Recommendation 4–8: **Studies on animals should be undertaken with particular emphasis on the detection of possible nonthermal and cumulative effects. Continuous, long term pulsed exposures should be emphasized. Frequency specific effects, influence of pulse repetition rate, peak power and average power density should also be studied.**

C. Cellular and Molecular Basis for Microwave Effects

Research is needed to determine the basic mechanisms of microwave alterations of cellular components and the locus of interaction of microwaves as a function of power density and frequency. Emphasis should be placed on developing a screening system for evaluating the effects of frequency variations with both pulsed and continuous exposure conditions. Instrumentation for generating and measuring microwaves will require further development for laboratory applications. Such equipment and applications will probably be very expensive to maintain and operate.

Research is also needed to investigate further the effects of microwave radiation on metabolic and genetic processes. Work to date has been mostly at power levels above 10 mW/cm^2 and has been restricted to several frequencies and continuous exposure conditions.

Recommendation 4–9: **Research is needed on the interaction of microwave radiation with tissues and cells in various organ and animal systems. Possible genetic effects of microwaves should also be explored. In addition, development of biological and physical dose parameters is needed.**

IV. Lasers

At the present time lasers are not an environmental health hazard to the general public to the degree that microwaves, noise, and air pollution may be; however, at the current rate of technologic progress, this may not be the case 5 to 10 years from now. The laser industry is approaching the 100 million dollar level annually and the potential applications of lasers are legion. In the future, lasers will be used to beam information over communication channels, ground to air and ship to ship, for airport traffic control, highway surveying alignment, missile guidance and interception around cities, and for art and holographic displays, etc., so there is the possibility that the general public will be exposed inadvertently. As of now, only special groups such as research workers, military personnel, and medical patients are subject to exposure, and only a few accidental exposures (approximately 10) have been reported (Crotin and Boyden, 1968).

The primary hazard from laser radiation is exposure of the eye; radiation levels, if kept below those damaging to the eye, will not harm other tissues and organs of the body (Ham, *et al.*, 1966). Tentative standards for permissible levels of radiation to the eye have been established for thermal damage, though there is a need for more research before these levels are generally accepted. The military services, several governmental agencies, and many industrial corporations have promulgated their own manuals and standards for laser safety and protection (Setter, *et al.*, 1968). Since the enactment of Public Law 90–602, there has been a movement towards standardization among the various services and agencies. It is probable that standards acceptable to all will be adopted by early 1970 through the Z–136 Committee on Laser Standards of the American National Standards Institute.

The applied research needed to perfect standards of permissible levels for thermal damage to the eye are well in hand and there is no need for extensive new efforts since adequate research support is being supplied by the Armed Forces and other agencies within the Federal government. There is meager funding for basic research in this area, however, and research presently being done is not concerned specifically with retinal thermal properties. The population at risk, while not large, is of special concern to the national interest. There is reason to believe that research capability in the field of visual function is adequate, if long-term support could be applied to study of chronic retinal effects of high energy radiation sources.

***Recommendation 4–10:* Support should be initiated for basic research related tc long-term thermal effects of visible, ultraviolet and infrared radiation on the eye. Included should be research on laser radiation as well as radiation from other optical sources.**

V. Heat, Cold, Humidity and Infrared Radiation

Heat exposure and mortality have long been linked. For example, Reyburn (1855) observed an association between intense summer heat and the occurrence of gastrointestinal disorders and Asiatic cholera in St. Louis. In one of the most disastrous summers of record, the Illinois Department of Public Health (1936) reported 9,423 deaths in July, 1936, as compared with 6,727 in July, 1935, an increase of 40%. Of the 1936 deaths, 1,193 were attributed to excessive heat, and the fatalities from heart diseases, apoplexy, nephritis, cancer and diabetes were 4,013 higher than in July, 1935. The increase in infant deaths was 20%. During the period 10–14 July, 1966, hot weather conditions in Illinois led to a 36% increase in deaths for the month over those that occurred in July, 1965, as reported by Bridger and Helfand (1968).

Prolonged exposure to dry-bulb temperatures higher than 28°C (65% relative humidity) may be considered hazardous to some individuals depending on

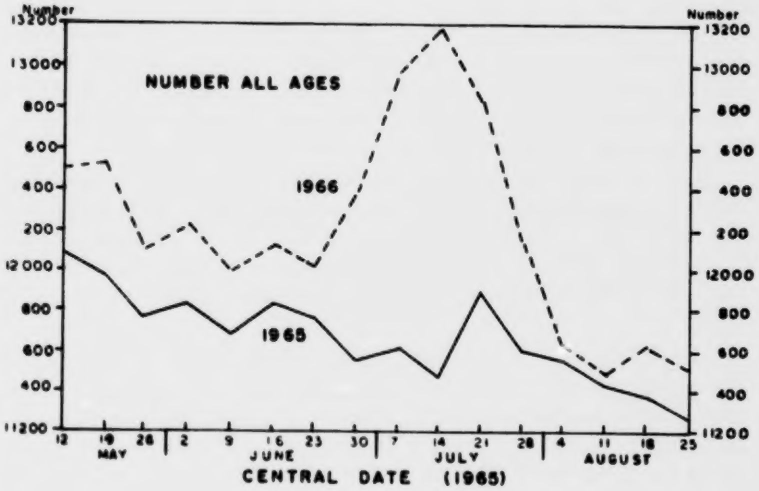

Figure 1. Three-week moving average number of deaths per week in 122 United States cities during 1966 July hot spell. 1965 data shown for comparison. (Reproduced by permission Int. J. Biometeorology and Drs. Bridger and Helfand).

age and physical fitness. The "comfort zone" for thermal exposure as set by the American Society of Heating, Refrigerating and Air-conditioning Engineers (ASHRAE) has upper limits of 25°C and 65% relative humidity and lower limits of 23°C independent of relative humidity between 20% and 80% for the normally clothed, sedentary individual living in the U.S. Generally acceptable standards do not exist for other indoor or outdoor environments or for other levels of activity (ASHRAE, 1969).

Cold exposure is often associated with respiratory and peripheral vascular diseases and is particularly dangerous to elderly people living alone. Quashnock (1967) notes that these individuals may develop spontaneous hypothermia and are first seen in the hospital with internal body temperatures of 30°C or lower. Complete recovery from such an episode is doubtful.

Exposure to very low or high water vapor pressures is associated with disorders of the skin and upper respiratory tract. Drying of the skin and mucous membranes of the nose in winter is a common experience and may be a predisposing factor to infection. Purchase of "humidifiers" in large quantities attests to the public concern with this problem. Exposure to high water vapor pressure in the presence of high temperature compromises sweat evaporation and may induce dangerous levels of hyperthermia. There are no standards for water vapor pressure (humidity) unrelated to the thermal comfort standard.

Infrared radiation refers to the portion of the electromagnetic spectrum between 800 and 100,000 nm wavelengths with the 800–3000 nm band known as the near infrared. The sun, steel-making furnaces, and other high temperature sources have a large part of their energy in the near infrared. Continued exposure to these sources can produce skin burns, cataracts and hyperthermia. Near infrared penetrates the optical system of the eye and may cause damage; long and medium range infrared is absorbed within 0.1 mm of the incident surface and thus heats directly only the surface tissues. There are no standards for infrared radiation exposure (Setter, *et al.*, 1968).

Taken together, heat, cold, humidity and infrared radiation represent the source of a wide spectrum of human ills that may be lumped into a single category called "thermal disorders" (Leithead and Lind, 1964). It is clear that there is a significant morbidity and mortality associated with exposures to heat and cold and that the means for treatment for these disorders, once they occur, are limited.

The epidemiology of thermal disorders has received little attention in the U.S. and thus the mortality due directly to thermal exposure is not known accurately (Bridger and Helfand, 1968). Leithead and Lind (1964) state that medical diagnosis of thermal disorders is uncertain and that the World Health Organization's classification of these disorders is inadequate. Even so, with the fragmentary data available, it is clear that every year thousands of people die and many more suffer from thermal exposure in the U.S. Public health standards for thermal exposure do not exist to assist in the planning of preventive measures.

Controlling the individual's microclimate is an important method of meeting the problem, but climate control prevents acclimatization, and for the unacclimatized individual the danger of heat stroke and other disorders occurs at temperatures easily tolerated by acclimatized persons (Leithead and Lind, 1964).

There are, therefore, serious health problems related to thermal exposures in the home and occupational environments which require a substantial effort. The principal problem areas are (a) lack of epidemiologic information, (b) the need for health standards for thermal conditions in housing and occupational environments, (c) the need for a better understanding of the psychologic and sociologic effects of prolonged thermal exposures, and (d) the need for a better assessment of the impact of future technologic developments on the thermal environment.

In view of the above, the Subtask Force considers that the biophysical, physiologic and medical effects of exposure to heat, cold, humidity and infrared radiation represent problem areas of urgent public health importance.

Recommendation 4–11: **Research should be promoted to study the effects of exposures to heat, cold, water vapor and infrared radiation on man and to develop biophysical and engineering methods for characterizing the thermal environment so as to enable the establishment of acceptable standards for climate control.**

Temperature, water vapor and infrared radiation interact with all other environmental factors. Air and water pollution, food preservation and infectious disease transmission are but a few examples. Bilharzia (schistosomiasis) is the largest single public health problem in Egypt today mainly because it is so hot that it is not possible to keep children from wading in the irrigation canals, where they pick up the infection from snails.

Because of our long familiarity with thermal factors in the environment, they are usually considered to be largely benign. However, with the growth of large concentrations of people in the "inner cities" of the U.S., the building of large power producers with associated excess heat, and the increasing concentration of CO_2 in the earth's atmosphere, the thermal character of the environment is being changed. The new problems thus developing must be met by those trained for an alertness to thermal dangers.

VI. Noise

A wide variety of sounds are encountered by man in his environment, some wanted and others unwanted. Wanted forms, typically of low level or otherwise controlled in strength and occurrence, convey useful information, induce desired moods and have other positive effects. Unwanted forms, relatively intense and intrusive, may cause adverse effects ranging from annoyance through interferences with purposeful activities to impairment of certain bodily functions. This section focuses attention on these latter adverse effects.

Unwanted sound or noise causes temporary and permanent losses in hearing, provokes physical and mental distress, hinders or complicates performance capability, and disrupts one's privacy, rest, relaxation, and sleep (Bell, 1966;

Cohen, 1968; Wilson, 1963). Noise-induced hearing loss is recognized as the most significant physical hazard caused by excessive noise, and there has been much research effort aimed at defining noise limits for safeguarding hearing (Kryter, *et al*, 1966; von Gierke, 1965). Numerous proposals for such noise criteria exist and some have now been incorporated in Federal and State occupational health regulations. Background noise specifications for rooms where speech communication is a vital function (e.g., classrooms, conference rooms) have also been prescribed based on studies of noise masking of speech (Webster, 1969). There are major gaps in knowledge concerning the non-auditory physiologic and psychologic effects of noise and their health significance. Too little sound, or a totally silent environment, also may have disturbing effects on man.

Noise exposures due to highly mechanized operations in industry (e.g., mining, construction, manufacturing) are generally of much greater intensity and duration than those typically experienced outdoors in the community or indoors in the home. Nonetheless, certain noises found in the latter environments reach levels comparable to those found at the noisier work places (Wilson 1963). Chief sources of community (outdoor) noise problems stem from transportation systems, construction-demolition activities, and trash collection. Major sources of indoor or home noise problems are power appliances (e.g., garbage disposal units, dishwashers).

Noise problems deserving study within a health framework can be broadly classified into three areas, namely, noise effects on physiologic functions, noise effects on performance and behavior, and considerations of noise annoyance.

A. Effects on Physiologic Functions

The effects of noise on physiologic functions can be subdivided into aural and non-aural categories. As already stated, noise-induced hearing loss is a major health problem and regulations are now in effect to curb such health hazards in industry. The criteria embodied in these statutes still lack wide acceptance among noise experts who believe that more information will be needed to justify limits prescribed for certain types of industrial noise exposures (e.g., intermittent exposure, impact and narrow-band exposures). Even the measure adopted for noise rating (A-scale in the latest Walsh-Healey legislation) has been questioned as to its efficacy in gauging the hazard of industrial noises of diverse spectra.

Recommendation 4–12: **Extensive surveys relating noise levels at work and length of occupational exposure to hearing sensitivity of worker groups exposed to representative types of industrial noise should be undertaken to resolve questions of hearing loss due to chronic exposure to noise.**

It is also becoming evident that the aggregate exposure to noise of modern living—i.e., noises from mass transportation, arrays of power appliances and power tools, and even hobbies and recreational pursuits—can cause some degree of hearing loss aside from that associated with the workplace. Noise-induced hearing change from these sources has important implications for concepts of "normal" hearing and judgments of occupational hearing loss (Ward, 1969).

Recommendation 4–13: **Studies characterizing non-occupational exposures to noise in relation to apparent temporary and permanent threshold shifts in the hearing of exposed populations need to be undertaken.**

Whether excessive noise can cause non-aural health disturbances is a matter of some conjecture and controversy. That noise can trigger cardiovascular, endocrine, respiratory, and neurologic changes suggestive of stress can be readily demonstrated (Broadbent, 1957; Grandjean, 1969, Jansen, 1969). At issue is whether repeated noise-induced changes of this nature ultimately have ill effects. The prevailing view of many noise experts is that man's tolerance to noise is high and most environmental noises can be adapted to without harmful consequences (Anthony and Ackerman, 1959; Wilson, 1963). Others maintain, however, that the stressful effects of noise, alone or together with other stress factors in the environment (e.g., vibration, heat), can overwhelm man's capability for healthy adjustment with resultant physical and mental health problems (Farr, 1967; Jansen, 1969). Scattered evidence for both points of view can be found, but in point of fact, crucial systematic evaluations of possible extra-auditory noise hazards remain to be undertaken (Jansen, 1961; Grandjean, 1969). Data here could corroborate findings from the European literature suggesting apparent links between work in noisy factories and cardiovascular-neurologic irregularities as well as social problems in the exposed groups (Jansen, 1961, 1969; Bell, 1966).

Recommendation 4–14: **Epidemiologic surveys should be undertaken of worker populations exposed to sustained, high level noise conditions in industry, and also residential populations living in areas subjected to significant noise intrusion from neighboring airports, roadways or industrial operations. The purpose of such surveys should be to determine whether non-aural physiologic effects exist.**

B. Effects on Performance and Behavior

Noises not intense enough to cause hearing damage or other physiologic effects may still disrupt speech communication, as well as the hearing of other desired sounds (Webster, 1969). Obviously, this disruption can degrade efficiency on jobs requiring reliable voice communication. However, noise effects on performance, not dependent on voice communication, are uncertain. Some studies have shown performance loss in noise, but others reveal no such loss or even improvement when compared to performance under quiet conditions (Broadbent, 1957; Cohen, 1969). The variable nature of these findings suggests the need for more controlled, analytical approaches to this problem with different factors referable to the noise, the task, and the subject performer being manipulated in single or joint fashion to determine possible noise-performance effects. Selection of tests or factors for study that are predicated on psychophysiological theory to explain performance effects of noise (e.g., arousal) would be particularly important here (Broadbent, 1957). Also deserving of close laboratory study are certain non-auditory sensory functions that may be altered by high level noise. Reported noise effects on the vestibular system, the vibro-tactile and thermal senses, and on certain aspects of visual preception need more systematic investigation in view of their implication to performance capability as well as accidents (Cohen, 1969). While certain physiologic changes initially evoked by noise do subside with recurrent exposures, suggesting adaptation, there are also indications that all functions do not adapt (von Gierke, 1965; Jansen, 1969). Further, adaptation for long-term exposures may produce important endocrine-metabolic deficits within the body which reduce its capability for coping with additional stresses, either increased noise or other physical stressors (Anthony and Ackerman, 1959).

***Recommendation 4–15:* Longitudinal or life-cycle studies of the physiologic and behavioral responses of animals to controlled amounts of noise need to be conducted in the laboratory to demonstrate whether there are cumulative effects from long-term exposure to non-traumatic levels of noise.**

C. *Annoyance Reactions to Sound*

Major causes of annoyance reactions to noise based on community surveys are startle reactions and interference with sleep (Wilson, 1963). Studies determining the effects of noise on sleep are just beginning, and much needs to be learned about types and levels of noise capable of disrupting sleep processes, the after-effects of repeated noise-sleep interruptions on one's physical and mental health state, and prospects for adaptation. Knowledge from such studies would have immediate value in specifying acoustic requirements in sleeping areas of dwellings. Definition of noise stimulus conditions provoking startle reactions and factors influencing adaptation of such reactions also require investigation. Previous conditioning to noise, the level of the noise, the level of the noise background, and the personality make-up of the receiver are factors deserving study apart from the startle stimulus itself.

The merits of different proposed acoustic measures for depicting the annoyance level of sound generalizable to all forms of environmental noise need to be evaluated. Having different schemes for rating the annoyance of noises originating from different sources has created immense confusion and efforts should be made to arrive at a single indicator for expressing noise annoyance level (Kryter, 1968). Correlations of annoyance level, as defined by these various measures, to physiologic changes might suggest some basis for deciding on an appropriate measure aside from subjective response.

***Recommendation 4–16:* Studies of sleep disturbance and startle reactions to noise should be initiated on an urgent basis owing to their implications for one's physical and mental health state.**

D. *Ultrasonic Energy*

Ultrasonic equipment is being increasingly used in applications such as cleaning, welding, medical diagnosis and therapy, and research. The problems of the biologic effects of ultrasound require considerable study and are exceedingly complex (Goldstein and Sinskey, 1969). Injury to tissue at therapeutic levels has been reported. The significance of lesser doses under chronic exposure conditions, as exemplified by ultrasound cleaners in industry and domestic applications, needs to be determined. Specific problem areas which need to be considered for research include the problems of *in vivo* hemolysis and the effects of ultrasound on developing tissues (such as growing teeth or bone) and on hearing.

There are currently no established guides for the safe application of ultrasound equipment in medicine or industry.

> ***Recommendation 4–17:*** **Research programs should be extended to provide a better understanding of interactions of ultrasonic energy with tissues and cellular components. Data on the effect of ultrasound on reproducing cells are needed to provide an insight into the significance of such radiation in various medical procedures and in setting standards for human exposure.**

VII. Vibration

The motions and stresses imposed by applying vibration, acceleration, and other transient forces on the human body can have different detrimental effects. Such forces can disturb sensory and neuro-muscular functions and thereby interfere with purposeful actions; they can damage tissue and organ structures, and induce feelings of fatigue, fear, and general discomfort (Goldman and von Gierke, 1961). Proposed safe limits for whole-body vibration exposures are based on tolerance judgments of human beings exposed to vibrations of various amplitudes and frequencies. There are marked discrepancies among the various limits proposed due to differences in rating procedures, and the inability to control key variables such as body posture, general muscle tone, and body type (von Gierke, 1965). Safe exposure limits for localized body vibration have not been specified.

As with noise, the more intense vibration-acceleration forces encountered by man are in the work environment. In particular, operators of heavy vehicles (tractor-dozers or trucks) and workers on or near heavy machinery in mills, factories and power plants probably experience the worst whole body vibration exposures. Heavy pavement breakers, rock drills, and other types of construction or demolition equipment also subject the operator to strong vibrational energies. The areas of exposure here are more localized affecting principally the hands, wrists, arms, and shoulders of the operators. Lighter, high-speed reciprocating riveters, and hand-held grinders and power polishers produce high frequency vibrations of small amplitudes. The effects of such vibrations are restricted largely to the contact areas of the user's hands and do not penetrate readily into body tissues.

The most significant form of public exposure to vibrations and other mechanical forces occurs in vehicle use. Such exposures are typically of low level, intermittent in nature and of short duration. The development of high-speed air, rail, and surface transportation systems, however, may raise problems of more severe vibration-acceleration exposures in the future.

A. Effects on Physiologic Functions

Only anecdotal evidence exists at present indicating acute and chronic injuries and disorders caused by vibration-acceleration conditions. There has been little effort to systematize the clinical data and to define the conditions that gave rise to them. Clearly, there is a need for epidemiologic work in this area. Initially, an attempt should be made to study physiologic disorders and health problems in those occupational groups experiencing high intensity vibrations.

Chronic injuries can also be produced by local vibration exposures as exemplified by a Raynaud-like syndrome in pneumatic hammer operators (Agate and Druett, 1947). Evidence suggests that different morphologic structures may be injured depending upon the frequency. Vibrations of low frequency (below 15 per second) seem to cause bone lesions and damage to tendons, neurovascular changes being more evident at medium and high frequencies (30 to 150 cycles per second) of vibration. Some evidence contradicts this generalization and may possibly be explained by the manner in which the equipment is held or used, and the position or strength of the grip. The significance of these factors is not known. Neither is much known about the physiologic mechanism responsible for these disorders, although mechanical, neurologic, and circulatory hypotheses have been proposed.

Recommendation 4–18: **Studies should be undertaken to establish relationships between levels of vibration or other mechanical forces in contact with man, durations of exposure, and evidence of acute and chronic injuries resulting from such exposure.**

B. Effects on Performance and Behavior

A number of studies have evaluated the effects of acceleration and vibration conditions on human performance, with apparent losses noted in tracking behavior, complex reaction time, and detection or vigilance capability (von Gierke, 1965; Ashe, 1961; Holland, *et al.*, 1965). There has been little or no effort to organize this information for predictive purposes. Questions remain, for example, as to what characteristic of vibration (e.g., acceleration, amplitude, frequency) is most critical in creating disturbance to a given activity?

Recommendation 4–19: **Research concerned with vibration-acceleration effects on performance should be extended.**

C. Annoyance Reactions to Vibrations

As already noted, judgments of the degree of comfort or annoyance experienced by subjects being vibrated at various frequencies and amplitides have been used to define limits for acceptable whole-body vibratory motions (Magid, *et al.*, 1960; Ashe, 1961). All such proposals suffer major limitations in that they do not adequately consider exposure duration and are concerned with only sinusoidal vibratory motion. Sinusoidal vibrations constitute only a small part of man's vibratory experience. Buffeting and jolting actions together with vibrations varying randomly in amplitude and frequency are more common occurrences. Attempts to evaluate directly the acceptance aspects for the latter types of exposure are meager, and extrapolations of such responses from simple vibration data are open to question. There is a need to monitor subjective reactions to assorted vibration conditions as a function of time. Indeed, indications of possible adaptation to early stages of a vibratory experience might be replaced with intense discomfort sensations later.

Recommendation 4–20: **Investigation of annoyance reactions to vibrations of different frequencies should be undertaken to determine if significant psychological effects can be demonstrated.**

VIII. Congestion, Crowding, and Isolation in Space Utilization

On the basis of preliminary evidence, abnormalities in the quantity and organization of the space available to a population can contribute substantially to emotional and intellectual incapacities among children; to increased aggression, withdrawal, and sexual abnormalities among adolescents and young adults; to higher incidence of "situationally derived psychological depressions" (Wilse, 1963) and perhaps schizophrenia (Zubin, 1963); and to higher accident rates and higher incidence of some transmissable diseases, especially rheumatic fever (Dodge, *et al.*, 1958). Crowding and isolation may also be factors in accelerated intellectual deterioration in old age and in increased mortality from arteriosclerotic heart disease (Fisher and Pierce, 1967; Kent, *et al.*, 1958). The Subtask Force did not consider population control as suitable for inclusion in its recommendations, but clearly such control is an important factor in the urgency of research on crowding and urban population growth.

Four reinforcing factors are thought to constitute the basis of space-associated biologic insults to man. The first is intense interpersonal competition for scarce resources, with the consequent stimulation of both aggression and fear. The second is the impedance of mobility and, in consequence, a reduction in the range and continuity of environmental stimulation. This in turn limits access to social networks and interactions needed for the build-up of critical information and effective behavioral strategies (Shimkin, 1968). Withdrawn children, in particular, may be subjected to the third factor of a "post-isolation syndrome" when thrust into competitive social contexts (Fuller, 1967). Such ineffective behavior would make more probable physical insults from aggression, accidents and psychosomatic illnesses.

The American Public Health Association (1950, 1960) has devised standards, from the standpoint of middle-class life ways, for optimal space allocations in household units and in neighborhoods, the latter being defined as the area served by an elementary school. In both instances, the standards are based on inventories of functions ("food preparation and preservation", "recreation and self-improvement", "education", etc.) consonant with high educational and health norms, small households, moderate fertility and high social controls.

For high-density public housing, Elizabeth Wood (1961) has proposed arrangements of space and function based on more realistic models and more heterogenous populations. Her designs seek to insure, for example, both privacy and social control through visibility for appropriate functions.

In all, the criteria cited are inadequate to provide useful standards for the design and utilization of indoor and outdoor space for two basic reasons. They propose standards far beyond possible attainment for today's poor, even in the United States. And they are based on "reasonable" intuitions, without a research foundation that would permit closer definition and variation in standards in accord with such controlling variables as (a) characteristics of the population (by age, sex, family, and household composition), (b) social values (e.g., housing and status) and degrees of political control over the population, (c) optimal circulation patterns and velocities, (d) socio-cultural heterogeneity and, (e) synergistic effects, e.g., maximum density variations under conditions of summer heat and winter snows.

Above all, the standards fail to define diagnostic criteria for transitions between *congestion* (without manifest developmental, social and physical hazards to a population) and a *crowding-withdrawal syndrome* with major health consequences. For these reasons, systematic research on the phenomena of space-population relations is an important task for research workers in the environmental health sciences.

The development of research on space-population relationships needs to be designed to meet three basic requirements. The first is the early identification of localities and populations where crowding or isolation syndromes are active or imminent. These include behavioral changes in children or adults, withdrawal in aged individuals, or aggressive behavior. For example, dormitory housing is probably an important type of stressful housing. It appears likely that the enormous growth of the American college population since 1960 has outstripped available housing, with the result being more intense dormitory and other group-quarters use.

The second requirement is the devising of pilot studies to develop the research tools capable of measuring significant health effects in these populations. The third is the formulation and testing of a cycle of research operations which would provide an adequate methodologic basis for establishing effective standards and procedures in regulating space-population relationships. This last requirement, which would start the replacement of empirical methods by those of a more rigorous nature, needs to be attacked. The essential goal here is to develop models, instrumentation, and procedures that would link the inherently partial results of particular approaches (such as animal experimentation or active research on human populations) into a coherent and productive system.

A moderate effort is needed to develop and standardize measuring techniques for field and laboratory use. A great deal already exists, but needs to be brought together and refined for better efficiency, reliability and acceptability. In general, while the mapping of static features presents few challenges, the elucidation of population characteristics, anticipations, social codes, loci, dysfunctions, and other behavior will be far more difficult, and new methods are urgently needed. Thus, new devices modeled on the urban-information cards developed by J. Voss and his students (unpublished) to gauge the capacity of individuals to cope with city complexities will be needed. Better indicators of health disturbances, easily reported and readily quantifiable, are also essential. High potentialities may be found in telemetering, e.g., via a transmitter in the heel of a child's shoe, to understand movements in relation to behavioral aspects. New monitoring equipment (TV, infra-red, etc.) can present far more meaningful aggregates of movement data than are presently possible. All of these approaches must not only be devised but utilized on a pilot scale in varying physical and social settings to establish their feasibility, acceptability by different populations, and their best uses. Training of personnel would also be part of the program.

Once the essential data from the pilot program have led to an effective general research capability, the effort should be expanded progressively into a more complete cycle and a larger scale of investigation. This could include the comparative, prospective investigation of selected areas (of census-tract size) exhibiting space-time-population relationships of a limiting type under varying cultural, spatial and geographic circumstances. The study of twelve to fifteen cases for two to three years could, with careful selection and a common methodology, yield a large body of complex information and suggestive hypotheses suitable for laboratory analysis with volunteer human subjects and, for testing extreme conditions with animal (especially subhuman primate) populations.

Recommendation 4–21: Research effort is needed to study the relationships of space utilization to physical and mental health by initiating studies which identify localities and populations where crowding or isolation syndromes are imminent, and to devise pilot studies to develop new research tools for detecting and measuring health effects.

IX. Barometric Pressure

The Subtask Force was not able to consider in detail the effects of altered barometric pressure on health. Although relatively small numbers of people are exposed to either very low or very high pressures, the problems associated with these factors are obviously of great importance to those exposed, usually in occupational or recreational settings.

At higher altitudes, lowered partial pressure of oxygen may give rise to significant health effects which may interact with other environmental agents. Effects have been observed on prenatal mortality, prevalence of certain disease states, and general mortality. For example, an increased hematocrit is part of the acclimatization process. Whether this fact could, by itself or in association with exposure to cold or other environmental agents, play a part in production of myocardial infarction is not known. One such agent that interacts with hypoxia is carbon monoxide.

The human population living at high altitudes is therefore exposed to special risks.

Recommendation 4–22: **Epidemiologic studies should be made to assess the long-term effects of residence of human populations at altitudes in the range of 4,000–11,000 feet. Special emphasis should be placed on congenital anomalies and on responses of the respiratory and cardiovascular systems, particularly as they may be modified by exposure to other environmental agents whose effects are likely to be enhanced by small degrees of hypoxia.**

X. Summary

The Subtask Force noted important deficiencies in research on physical factors in the environment, particularly with respect to noise, heat, crowding and radiation. One of the major deficiencies is the marked dispersion of responsibility in this field at the Federal level. In the opinion of the Subtask Force, primary responsibility for research in this area should be assigned to a specific agency and higher priority should be given to research into all aspects of physical hazards in the environment.

With respect to ionizing radiation, the Subtask Force believes that additional research is needed to support the control programs currently underway within the U.S. Department of Health, Education, and Welfare. Problems cited as needing attention include those associated with increasing population exposure to medical sources as well as radionuclide releases from nuclear reactors and nuclear fuel processing plants. Specific research areas of need include investigations of the mechanisms of action of ionizing radiation at the molecular and cellular level (Recommendation 4–1), better definition of the theoretical basis of dose-response relationships for genetic and somatic effects (Recommendations 4–3 and 4–4), obtaining greater knowledge of radiation repair processes and the fundamental nature of aging (Recommendation 4–5), and the development of techniques for the dosimetry and evaluation of tissue effects of intense localized sources (Recommendation 4–6). Lastly, the Subtask Force calls for a continuing effort on epidemiological studies and the establishment of a national depository for pertinent information (Recommendation 4–2).

The Subtask Force acknowledged that, although the magnitude and extent of pollution of our environment by microwave radiation has not been systematically evaluated, it can be conservatively estimated that nearly one-half of the U.S. population lives in a measurable microwave environment. Exposure standards in the United States are based primarily on the thermal hazards associated with microwave exposure. Standards developed in the Soviet Union and other Eastern European countries, on the other hand, are based on non-thermal biologic effects. It is significant to note that exposure standards of the latter countries permit a level one thousandth of that accepted in the United States. To determine the role of non-thermal effects of microwaves, the Subtask Force calls for epidemiologic investigations of the effects of microwave radiation on man (Recommendation 4–7), studies on animals with particular emphasis on the elaboration of possible non-thermal and cumulative effects (Recommendation 4–8), and research on the interaction of microwave radiation with tissues and cells in various organ and animal systems (Recommendation 4–9). Although lasers and ultraviolet radiation sources are not considered a major environmental health problem at the present time, the Subtask Force believes that basic research on possible effects of these sources on the eye are needed (Recommendation 4–10).

Excessive heat and cold remain significant causes of health problems and lethal effects of excessive heat are easy to demonstrate. The Subtask Force believes that this is an area of research which has not had adequate attention. Even though some control of exposures is possible, there is not an adequate basis of understanding for standards to be set. In particular the Subtask Force noted that there are no standards for water vapor pressure (humidity) unrelated to the thermal comfort standard and that there are no standards for infrared radiation exposure. To correct these deficiencies, the Subtask Force recommends that research be promoted to study the effects of exposures to heat, cold, water vapor and infrared radiation on man and to develop biophysical and engineering methods for characterizing the thermal environment (Recommendation 4–11).

Some community or non-industrial noise levels are beginning to reach the intensity associated with hearing defects in occupational groups. There are also indications that significant non-aural effects of noise may be accruing to large urban populations. To resolve questions of hearing loss due to chronic noise exposure, the Subtask Force recommends that extensive surveys be made to relate industrial noise levels and length of occupational exposure to the hearing sensitivity of exposed worker groups (Recommendation 4–12) and that studies be undertaken to characterize non-occupational exposures in relation to apparent temporary and permanent threshold shifts in the hearing of exposed populations (Recommendation 4–13). The Subtask Force also recommends that epidemiologic studies be undertaken of worker and residential populations to determine whether non-aural physiologic effects exist (Recommendation 4–14) and that longitudinal or life-cycle studies be made of physiologic and behavioral responses of animals to controlled amounts of noise (Recommendation 4–15). Because of the implications of noise annoyance in terms of man's physical and mental health state, the Subtask Force urges that high priority be given to startle reactions and to studies of noise disturbance to sleep (Recommendation 4–16). The Subtask Force also recommends that research programs be extended to provide a better understanding of the interactions of ultrasonic energy with tissues and cellular components (Recommendation 4–17).

It was noted that motions and stresses imposed by applying vibrations, accelerations, and other transient forces on the human body can have detrimental effects. Such forces can disturb sensory and neuro-muscular functions and thereby interfere with purposeful actions and can damage tissue and organ structures and induce feelings of fatigue, fear, and general discomfort. The most significant form of public exposure to vibration and other mechanical forces occurs in vehicle use. As with noise, however, the more intense vibration-acceleration forces encountered by man are in the work environment. To clarify the situation with respect to this physical stress, the Subtask Force recommends that studies be undertaken to establish relationships between levels of vibration and durations of exposure and evidence of acute and chronic injuries (Recommendation 4–18), that research on the effects of vibration-acceleration on performance be extended (Recommendation 4–19), and that investigations of annoyance reactions to vibrations of different frequencies be undertaken to determine if significant psychologic effects can be demonstrated (Recommendation 4–20).

Although research on crowding, congestion, and isolation in physical space is a field not usually considered the responsibility of health agencies, there is evidence that this represents a major health problem particularly in terms of behavioral disturbances. One of the primary needs is to develop adequate research methods to study the relationships of space utilization to physical and mental health. In this connection, there is a need to identify at an early stage those localities and populations where crowding or isolation syndromes are active or imminent, to devise pilot studies to develop research tools capable of measuring significant health effects in these populations, and to formulate and test a cycle of research operations which will provide an adequate methodologic basis for establishing effective standards and procedures in regulating space-population relationships (Recommendation 4–21). Also needed is an effort to develop and standardize measuring techniques for field and laboratory use in this area of research.

The Subtask Force was not able to consider in detail the effects of altered barometric pressure on health. Nonetheless, increased research and epidemiologic studies were recommended to assess the long-term effects of residence of human populations at altitudes in the range of 4,000 to 11,000 feet. Special emphasis should be placed on congenital anomalies and on responses of the respiratory and cardiovascular systems (Recommendation 4–22).

BACKGROUND DOCUMENTS

Document Number	*Author*	*Title*
PF–1	Cohen, A.	Sound and Vibration.
PF–2:I	Ham, W. T. and Cleary, S. F.	Considerations in the Evaluation of the Biological Effects of Exposure to Microwave Radiation.
PF–2:II	Ham, W. T. and Clarke, A. M.	Lasers.
PF–3	Hardy, J. D.	Heat, Cold, Water Vapor and Infrared Radiation.
PF–4	Shimkin, D. B.	Space, Congestion, Crowding and Isolation: Preliminary Analysis of Problems and Potential Research.
PF–5	Hasterlik, R. J.	Ionizing Radiation.

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PART III

RECOMMENDATIONS FOR RESEARCH ON METHODS AND SPECIFIC DISEASE CONDITIONS

Chapter 5 Epidemiology and Biometry

Chapter 6 Epidemiologic Aspects of Carcinogenesis

Chapter 7 Carcinogenesis, Mutagenesis, and Teratogenesis

Chapter 8 Toxicology

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Chapter 5

EPIDEMIOLOGY AND BIOMETRY

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EPIDEMIOLOGY AND BIOMETRY*

I. Introduction

There is a close interdependence of the fields of epidemiology and environmental health. Data on man himself, when available, provide the soundest basis for assessing the effects of environmental contaminants on human health. To the extent that programs of environmental control or modification derive their impetus from health effects, they therefore depend for their rationale very much on the resources and skills of the epidemiologist. To a comparable degree, in elucidating the etiology of diseases of unknown cause the epidemiologist is dependent on the observations of those concerned with the quantitative and qualitative description of the human environment.

During recent decades there has been a considerable expansion of knowledge of the physical, chemical, and biological contaminants of man's environment. This has prompted demands for information which would allow assessment of the possible health effects of the observed contaminants. It has become apparent that current epidemiologic resources are inadequate to answer the many questions that have been raised. Deficiencies exist in available manpower, in sources of relevant data and in the sophistication of techniques of biometric analysis. These problems are of concern to governmental and non-governmental agencies other than NIEHS, but NIEHS is certainly one of the major agencies whose mission would be greatly facilitated by a general strengthening of epidemiologic resources.

In this report our considerations have not been limited to aspects of epidemiology that are the exclusive concern of NIEHS—indeed, there probably are no such aspects—but our discussions have been oriented toward matters that seem most directly pertinent to the problems discussed by the Task Force.

II. Routine Sources of Data on Health Status

Detection of health effects of environmental change requires the availability of data which can be analyzed periodically to describe variations in health status over time or between areas or among segments of the population. Such data may also serve as the starting point for more detailed analytic studies, but in this section of our report we are concerned with their use for routine surveillance purposes.

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* This chapter was prepared by a Subcommittee chaired by Dr. Brian MacMahon and co-chaired by Dr. Ian T. T. Higgins. Individuals who contributed to the information presented included Drs. Arend Bouhuys, Morton Corn, Philip E. Enterline, Benjamin G. Ferris, Jr., Bernard G. Greenberg, and Robert J. Hasterlik.

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Insofar as mortality is concerned, existing sources of data in this country are reasonably satisfactory. Preliminary tabulations, based on death registrations, are produced and published rapidly and at short intervals by the National Center for Health Statistics (NCHS), and quite detailed analyses are published annually. There are, of course, deficiencies in certification—particularly with respect to cause of death—and limitations resulting from the selection of a single "underlying cause" as the basis for tabulation. These and similar problems are being seriously attacked by NCHS, and mortality data should become increasingly accurate and useful.

Occupational mortality statistics in the U.S. are, however, regrettably inadequate for even a preliminary assessment of the occupational risks of different diseases. Mobility of the population and frequent job changes complicate the collection of the required information, but to some extent inaccuracy of comparisons of the risks experienced in different occupations is due to lack of comparability in the manner information on occupation is collected at the census and at death. Little effort seems to have been made to improve this situation. Collection of occupational information should continue and a serious attempt should be made to improve its accuracy.

With respect to morbidity, the picture is generally unsatisfactory. There is at present no program for the routine, periodic publication of illness rates based on medical diagnoses in a defined population. The interview component of the National Health Survey is ongoing but is based on the interviewee's own understanding of his diagnosis. The examination component of the survey is not planned as an ongoing program, and, in any event, provides prevalence, not incidence, data. Various insurance and medical care plans might be able to provide such data, but do so only on an *ad hoc* basis, if at all.

The Subcommittee discussed the advisability of setting up a large-scale program of disease surveillance—perhaps combined with close environmental surveillance—in selected areas of the country. It has been suggested that areas could be chosen to represent urban and agricultural settings and areas of high and low levels of environmental contaminants of various kinds. The Subcommittee considered that the time is probably not ripe for such an undertaking. Geographic areas with widely different levels of individual contaminants are not easy to find in this country, and the problem of selection of areas is vastly compounded when the number of contaminants of potential interest is considered. Nor do ideas yet seem clear as to what health measures would be most appropriately incorporated into such a "sentinel" system. Recent experience in other fields where large-scale studies have been set up to allow correlation of almost any conceivable cause with any conceivable effect, has not been such as to encourage further efforts of this kind.

The Subcommittee also considered the possibility of more limited surveillance systems operating through routine processing of hospital data in defined populations. While strongly supporting the development of such systems, the Subcommittee had no specific recommendations to make, since the problem is already under very active consideration by various medical care insurance plans, the Regional Medical Program, and other agencies. It seems likely that rates of hospitalized illness in selected, defined populations will be available in the near future.

Notification of specified infectious and occupational diseases is a further method of disease surveillance which needs to be considered. Such methods have not been particularly popular with physicians in this country; consequently, they have been largely ineffective and unrewarding. A case might, however, be made for an intensive campaign in one or two areas of the U.S. to make these measures as complete, accurate and comprehensive as possible with a view to evaluating the possible benefits of an effective system.

The desirability of stimulation of more registries of specific diseases was considered. Registries as depositories of data serve only to alleviate the unemployment problem—and even that to only a trivial degree. But a well-organized registry can serve not only as a surveillance mechanism but as a point of departure for effective analytically oriented research. The effectiveness of a registry depends on the completeness with which all cases occurring in a defined population are reported, the accuracy of the information received, the efficiency and rapidity with which the data can be processed and published, and, probably most important of all, the existence of a group of investigators deeply interested in exploiting the data for research purposes. It should also be mentioned that a disease registry becomes more useful the longer it has been in existence, provided that names, addresses and other information are regularly updated.

The cancer registry of the State of Connecticut is an example of an active registry that has been effectively used for a variety of epidemiologic purposes. One fully exploited registry is preferable to several inadequately utilized; additional cancer registries do not seem to be particularly needed at the present time, at least in geographic areas ecologically similar to Connecticut. Given the interest of a local research group, there may well be justification for the development of a cancer registry in ecologically distinct areas, for example, the Southern United States or Hawaii, or for strengthening the existing registry in Puerto Rico.

A group of diseases for which registration has been much discussed, but not yet implemented in this country, is the congenital malformations. There is abundant evidence that the great majority of congenital defects have an environmental component to their etiology. Causes so far identified in man include examples of physical, chemical, and biologic agents, although the known agents account for only a very small fraction of the cases. An effective registry could serve both as a surveillance system to detect new environmental teratogens and as a base for etiologic studies. Either one of these functions alone would justify the establishment of a registry.

Recommendation 5–1: **The establishment of one or more ongoing registries of congenital malformations in the United States is a matter of some urgency. The registry should cover a defined population, and should include all congenital malformations, whether diagnosed at birth or later in childhood. The registry should be established in close**

association with an active research group, and its funding should provide for the full exploitation of the data for research purposes.

The above recommendation, which is directed specifically to the study of environmental factors in malformation, should be considered in conjunction with the recommendations of the Subcommittee on Carcinogenesis, Mutagenesis and Teratogenesis regarding the detection of genetic changes (Chapter 7).

A strong case can also be made for the use of registration as a research method both for identifying persons with certain rare diseases as a preliminary to further study, and to obtain a roster of persons exposed to some environmental agent, whose hazardous nature requires further investigation.

III. Special Surveys

A. Studies in Community Settings

Readily available data do not, and probably never will, provide all the information needed either for the surveillance of the health of populations or for assessing the role of environmental exposure in the causation of disease. Special surveys will continue to be essential for studies of problems that are not accessible through routine sources of data. Such surveys may be cross-sectional, longitudinal or a combination of both. The choice will depend on the goals of the investigation. More important, however, than the type of survey, is selection of the population for study; for example, hospital patients, occupational groups or segments of general communities. In this country the largest survey effort is the Health Interview Survey of the National Health Survey, in which a representative sample of families in the U.S. is interviewed each month. As noted above, the information obtained comes solely from the respondent. There is a need for information of this nature based on medically confirmed diagnoses.

On a smaller scale, intensive surveys have been carried out by many investigators. Some of these studies have been essentially cross-sectional in design, others have been longitudinal. A useful approach involves follow-up of a sample that had previously been the subject of a cross-sectional study, particularly when the follow-up is combined with a new cross-sectional study to measure any cohort changes. The methods used in these surveys have varied and tended to include a number of standardized tests. They have included questionnaires, physiological and other tests, sometimes clinical examinations and usually a careful appraisal of several environmental factors. It is, of course, essential that information on personal characteristics and other factors related to the disease under study should be included.

1. Survey Design

The investigator should indicate clearly which particular environmental factors are to be studied and should use appropriate measures for estimating exposure as accurately as possible. Some of the problems of estimating exposure to air pollutants are indicated in the report of the Subtask Force on Air Pollution (Chapter 1). The possible effects of exposure which need to be considered include mortality and morbidity, preclinical evidence of disease as revealed by symptoms and special tests, and physiological, biochemical or psychological impairments or deviations from some established norm. Every effort should be made to ensure that the information which is obtained in the survey is of the highest quality. To this end the investigator needs constantly to try to develop new methods and refine old ones to characterize more precisely the relevant causative factors and the biological responses to them.

Surveys of this kind need to be carried out in the general community as well as in specific occupational groups. Surveys in the general community are also essential in order to establish soundly based standards of normality and to measure the risk of chronic low levels of environmental exposure accurately.

The epidemiologist should also be alert to the possibility of exploiting a natural experiment such as that resulting from an accidental exposure. A good recent example has been the extensive studies of the populations exposed to fallout from atomic explosions. Assessment of the effects of occupational accidents or of the several episodes of acute air pollution are others.

Evaluation of any control measures which may be introduced can also often throw light on the etiological role of an environmental hazard. The possibility of conducting surveys in such an experimental or semiexperimental situation should be considered more often than is usually the case.

> ***Recommendation 5–2:*** **Well designed surveys of special population segments, including representative samples of the general community, are important in elucidating the effect of environmental hazards. Such surveys deserve continuing support.**

It is important to recognize that many problems require observations over very long periods of time. Opportunities should therefore be sought for continued observation of groups that have already been under longitudinal study for other purposes. The previously cited Japanese populations, under detailed study by the Atomic Bomb Casualty Commission for almost 25 years, provide opportunities for studies of many health problems other than the question of radiation effects.

> ***Recommendation 5–3:*** **Efforts should be made to preserve and continue to develop health information on populations that have been under detailed observation for specific purposes. Particular interest would be in populations where environmental measurements have also been made.**

B. Studies in Occupational Settings

Populations in industry have long been used to study factors associated with health. There is ample basis to recommend continuation of this emphasis within NIEHS and other agencies. It is recognized that the health experience of these populations must be related to social, biological, and host factors, as well as to physical aspects of the environment.

1. Opportunities

Industrial populations offer good opportunities for prospective studies because:

a. Large segments of the population work regularly. The populations selected can be classified by age, sex, and other factors, as well as by nature and extent of exposure.
b. The work environment can be reasonably well defined and will become better characterized in the future if an Occupational Health and Safety Act is passed by the Congress.
c. Where periodic medical examinations are done on workers, more detailed data relative to "health" are available. Such data might be used to characterize individuals who were unavailable for special studies. However, increased emphasis must be placed on the quality of periodic examinations if such data are to be used for research purposes.
d. Industrial record keeping may provide data on residence, family history and structure, and other facts which may be useful in investigating environmental factors.

2. Limitations.

At the same time, studies of occupational populations have certain limitations:

a. The accuracy of extrapolation to general populations may be limited because of selection of workers by industry, selection of industry for study, selection of industry by the worker, and selection by the worker of a particular job within the industry.
b. Workers previously disabled or retired will not be available in samples selected from lists of current employees. The missing will, of course, include an unduly high proportion of affected persons.
c. Persons who choose, or are able, to remain in a particular occupation may be those least sensitive to the exposure associated with it—for reasons not directly related to the outcome under study. Consequently, if no disease or effect is identified in an occupational group, it cannot be assumed that there will be no effect of comparable exposures in the general population. And if effects are identified in occupational groups, they may be more prevalent or extensive if the population contains a higher proportion of sensitive individuals.
d. Components of the environment other than the predominant component under investigation may be different in the occupational and community populations, making extrapolation from one to the other unreliable.

Recommendation 5–4: **Every advantage should be taken of the opportunities provided in industry to study the relationship of disease to both external factors and the characteristics of workers. NIEHS and other agencies interested in environmental health should foster ties with industry and labor groups to initiate prospective, as well as retrospective, studies. Special situations of high exposure, as may exist in other countries should be fully exploited.**

Recommendation 5–5: **Research is needed into the nature of the psycho-**

logical and physical factors influencing choice and retention of specific occupations. It is possible that animal experiments on natural selection associated with various stresses will be helpful in such research.

IV. Problems in Design and Conduct of Analytic Studies

A. Basic Procedures

Under this heading, consideration is given to studies in which the frequency of disease and physiological, biochemical and psychological deviations from a norm are related to a specific environmental exposure. At least two procedures are involved:

a. The identification of the individuals exposed, and to the extent possible, the quantification of their exposure.
b. The determination of whether the individuals experience the health effect being evaluated.

1. Social Security Records.

In the United States, both of the above procedures present difficulties, but the size of the country, its multiple jurisdictions and the mobility of the population make procedure 'b' a particularly vexing problem. An important source of follow-up information at the national level for subjects with known Social Security numbers has been through records maintained by the Social Security Administration. These have been used primarily to identify deaths, although they have also been used in a few instances to identify persons who retire before the normal retirement age because of disability. In these cases, the records have also been used to identify the cause of the disability. Since the record system maintained by the Social Security Administration was developed primarily to determine eligibility for Social Security benefits, and to record insurance payments, its use in follow-up studies is cumbersome and time-consuming. In many instances in which a retirement or disability claim is filed, the fact of subsequent death can be determined only by examining files at regional payment centers. In most cases information on cause of death cannot be supplied by the Social Security Administration and various state and local health department records need to be searched in an effort to obtain a death certificate.

Two changes in the Social Security records would greatly facilitate epidemiologic investigations:

a. All deaths should be recorded centrally and appear on the master tapes maintained in Baltimore.
b. These records should be linked with death certificate data maintained by the National Center for Health Statistics in Washington, D.C.

Recommendation 5-6: **The National Institute of Environmental Health Sciences should approach the Social Security Administration to determine under what circumstances Social Security record can be used for epidemiologic studies, and what administrative and financial mechanisms might be set up to improve access to the data for follow-up purposes.**

For a variety of reasons, Social Security files may not provide a ready means of follow-up for particular cohorts of interest. In such instances, and if death is the outcome under investigation, the fact of death can be determined only if the State in which it occurred is known to the investigator. While alphabetical indices of deaths are maintained by the various health departments, there is no national centralization of these indices. A central national index would greatly facilitate studies in which the outcome of concern was one involving a high probability of death.

> ***Recommendation 5–7:*** **A national death index should be established by the National Center for Health Statistics. The index should provide the identifying information necessary to locate the death certificate filed in the States and other Registration Areas.**

2. Other Data Sources (*Record Linkage*).

Further exploration is needed of other national sources of data in follow-up studies. Social Security numbers now provide access to income tax returns and the filing of these for any given year can be used as an indication of continued survivorship in follow-up studies and their potential should be further developed and explored. In the future, medical-care records such as those maintained by Blue Cross, Medicare, and Medicaid will become increasingly useful as coverage of the population by these plans expands. The increasing use of the Social Security number as the identifying number in such plans provides a strong argument for the use of this number as the individual's unique identifying number—to be used in identification of hospital and all other medical and social records—to facilitate the computer linkage of records for research purposes.

It is noted that a subcommittee of the National Committee on Vital and Health Statistics (Public Health Service, 1968) has previously recommended the use of the Social Security number for all record purposes, and also the formation of the National Death Index referred to above.

> ***Recommendation 5–8:*** **Interagency cooperation is urged to foster the development of specific record linkages that will facilitate the detection of health effects of environmental contaminants.**

The Subcommittee wishes to draw attention to a very significant resource for epidemiologic studies requiring long-term follow-up. This is the Follow-up Agency of the National Academy of Sciences—National Research Council (De-Bakey and Beebe, 1962). This agency exploits the records of the Armed Services and the Veterans Administration, as well as the reports of deaths of veterans received in connection with claims for death benefits, to make long-term linkages between exposures and death rates by cause. The exposures capable of study include those received in civilian life as well as those encountered during the military experience. The continuation of this agency is dependent on the support of agencies to whom its resources are relevant.

> ***Recommendation 5–9:*** **NIEHS and other agencies interested in environmental health should explore with the Follow-up Agency of NAS-NRC the kinds of consultation and financial support necessary to ensure the**

utilization of the resources and experience of the Follow-up Agency for the investigation of problems of significance to their goals.

B. Statistical Analysis

There is considerable room for improvement in the statistical techniques currently being applied in the analysis of epidemiologic data. Among the areas of particular concern to the Subcommittee are the following:

1. Time Series.

Large volumes of data will be accumulated in systems of surveillance and at monitoring stations. Also, repeated measurements of physiologic performance are likely to be made on groups of individuals. In both cases the problem of analyzing data from a time series is a difficult one because the observations are not independent of those made at prior points in time. These autocorrelations require special tools of analysis and further study needs to be made of these problems.

2. Longitudinal Studies.

Long-term studies will be needed to measure the human response to low levels of exposure occurring in varying quantities over long periods of time. The analysis of longitudinal data not only involves the problem of time series analysis mentioned above, but the measurements of cohort and temporal effects. The largest body of methods for the analysis of longitudinal studies was developed in connection with growth studies. Little has been added since to keep up with new developments in nonparametric statistics and multivariate analysis. Furthermore, models of disease can be developed and tested in longitudinal studies, and there is need for this kind of modeling in environmentally caused diseases.

3. Multivariate Methods of Analysis.

In view of the lack of sensitivity of some of the measures of human response, there will usually be a host of dependent variables relating to outcome. Similarly, there will be measurements on a large number of precipitating etiologic factors including various ones in combination. The appropriate analysis of such relationships requires a multivariate approach if the interactions are to be studied and the effects of all responses are to be pooled.

4. Statistical Estimation.

The technique known as Bayes estimation needs further study in the area of epidemiology. The Bayes estimate attempts to incorporate prior knowledge about a parameter or its probability distribution into new estimates of the statistical measure. In environmental health sciences, research is needed to learn how to use Bayes estimation techniques so that all bits of meaningful information can be combined into one estimate.

5. Contingency Tables.

Finally, an old problem which needs further work is the analysis of the usual contingency table. The question of how best to measure the strength of an association between an environmental factor and a response variable is still not completely answered. Data from the environmental health sciences would be useful to create models for analysis in the same way that much was contributed by the data from the cigarette smoking-lung cancer controversy.

Recommendation 5–10: **The development of more efficient statistical techniques for analysis of epidemiologic data should concern NIEHS as much as does the development of more effective methods of measuring environmental contaminants. To this end, support should be provided for basic biostatistical research.**

V. Computer Simulation Studies

Demographic microsimulation models have been developed in recent years to study the effects of changing patterns in population growth. The computer is used to generate from an initial population a complete vital history of each individual taking into account all the competing risks to which he is exposed. The models are usually stochastic, since random sampling of probability distribution determines which events occur and at what time. The models are also dynamic in nature since they allow the probabilities to change with time and thus permit a feedback mechanism.

There are problems in epidemiology where similar approaches would be beneficial. For example, one may wish to study the nature and effect of the selection bias that occurs in an industrial setting where:

1. Workers less resistant to pulmonary stress are more likely to leave employment in a factory where there is air contamination, and
2. Workers who remain are subject to an increased risk of mortality from certain respiratory diseases after a lapse of time.

With given parameters for these two conditions, one could calculate the bias inherent in a surviving population at ages 50, 60, and retirement. In a similar manner, one could simulate the problem of tracing individuals in longitudinal studies or the biases which migration creates when individuals with symptoms move away from an area according to a given probability distribution.

Recommendation 5–11: **Work in computer simulation of problems in the field should be stimulated and supported by NIEHS and other agencies concerned with environmental health.**

VI. Manpower and Training

Although the report of the Task Force includes a section (Chapter 11) devoted to recommendations for meeting training needs in environmental health, the Subcommittee on Epidemiology and Biometry considered the problems of meeting manpower needs for epidemiologists so important that suggestions for solving this problem are discussed as a separate item in the paragraphs to follow. Included are both a review of the qualifications for scientific personnel to meet these needs and recommendations for action on the part of the National Institute of Environmental Health Sciences.

The epidemiological approach to problems in environmental health is similar in many fundamental aspects to the epidemiologic approach in any disease situation. The basic assumption is as follows.

There is an etiological cause-effect relationship existing in this area of concern and this can be expressed by a dose-response curve. Once an etiologic relationship is established, preventive actions can be initiated by an appropriate allocation of resources.

The basic difference from the epidemiologic approach to the study of infectious diseases is in the nature of the environmental agent and the exposure to the agent. Not only is the cumulative amount delivered of a different order of magnitude, but a complex problem arises in design and analysis because of the varying amounts of exposure, which are generally at low levels and over long periods of time. These difficulties create special problems in delineating the cause-effect relationship. There is also challenge to the environmental health specialist in the science of mensuration to detect low levels, particularly on some automatic basis adaptable for monitoring. Finally, there is the challenge to the biostatistician in problems of sampling over space and time as well as in methods of analysis.

To meet the needs of this field, it is proposed that a new kind of specialist called an Environmental Epidemiologist be trained. The curriculum should include strong emphasis in epidemiology, environmental health sciences (e.g., aerometry and toxicology), and biostatistics. The training might be done by pooling the efforts of these three major disciplines plus others such as the social and behavioral sciences. Recruits could come from any one of these three disciplines. The thrust of the training might be in the discipline of professional training with strong minors in the remaining two. An alternative approach would be a complete interdisciplinary effort where the training was equally divided among the disciplines.

In addition to changing the nature of the training received by workers in the epidemiologic aspects of environmental health, it should be noted that this proposal for training environmental epidemiologists broadens the base for recruitment into the field. It is apparent that the manpower needs in this field will never be satisfied if entry is restricted to physicians and an occasional statistician. This limitation is maintained not only by tradition but also by certain Civil Service regulations. The latter should be eliminated.

Recommendation 5–12: **NIEHS should stimulate and support the training of environmental epidemiologists along the lines indicated above. At the same time, support of more traditional training in epidemiology and biometry should be considered appropriate to the objectives of NIEHS.**

Recommendation 5–13: **The Public Health Service should seek elimination of the Civil Service regulation restricting the position of "epidemiologist" in the Federal Service to persons with medical qualifications.**

Since physicians will no doubt continue to form the bulk of recruits into epidemiology, every effort should also be made to expand recruitment from medical schools. In this connection, experience in other fields has demonstrated the utility of providing opportunities for medical students to undertake elective and summer training in the field.

> ***Recommendation 5–14:*** **Opportunities should be provided for medical students to take elective and summer work in the Environmental Health Centers, in Departments of Epidemiology and Biometry, and at NIEHS and other governmental agencies concerned with environmental health.**

VII. Summary

Routine sources of data in the U.S. are inadequate for studying possible relationships between environmental exposures and disease or disability. Mortality statistics provide useful information on highly fatal diseases, but the need is much broader than this. Morbidity statistics are even less satisfactory. More comprehensive reporting of hospital admissions, such as is now being considered by various insurance systems, Regional Medical Programs and other agencies, is desirable. Cancer registries have proved invaluable in studies of this disease. Existing cancer registries should be improved and fully exploited before new ones are established. However, the establishment of a registry of congenital malformations in a defined population, to be used for surveillance and research into etiology, is recommended (Recommendation 5–1).

The Subcommittee did not consider that the time was ripe for a large-scale combined program of disease and environmental surveillance. Instead they favored specially designed surveys, in which environmental exposures are defined and measured as appropriately and accurately as possible and related to indices of disease such as mortality and morbidity, or to physiological, biochemical and psychological impairment or deviation from a norm. Surveys of this kind should be considered in occupational groups as well as in the general community. Often, considerable light can be thrown on the role of an environmental factor in the causation of disease by a cross-sectional study. But, more often, prospective observations are required to estimate the risk accurately. While it would be desirable to conduct such studies in the general community, they will usually be more practicable in more stable occupational groups (Recommendations 5–2 through 5–5).

Follow-up of populations exposed to a possible environmental hazard presents particular difficulty in this country. One source of information is the Social Security Administration. The use of such information for medical studies is limited by confidentiality of the records. The Subcommittee recommended that an approach should be made to the Social Security Administration with a view to devising means of increasing the availability of Social Security records for follow-up studies, while satisfying the criteria of confidentiality. Another source of information which has been highly valuable for long-term follow-up studies is the Follow-up Agency of the National Academy of Sciences, National Research Council. A further recommendation is the establishment of a National Death Index to facilitate the location of death certificates of persons for whom the date or place of death is unknown. The increasing use of Social Security number as a unique identifying number should be encouraged. Ultimately, this should lead to the establishment of a record linkage system in this country such as those currently being developed in other countries (Recommendations 5-6 through 5-9).

Apart from the conduct of epidemiological studies, there are still also major problems in their analyses. Further research on methods of analysis of longitudinal data, on multivariate analysis and on epidemiological models, including computer simulation, is indicated (Recommendations 5-10 and 5-11).

To meet the needs for trained environmental epidemiologists, the Subcommittee recommends that the National Institute of Environmental Health Sciences stimulate and support training in this field, that the Civil Service regulation restricting the position of "epidemiologist" to persons with medical qualifications be eliminated, and that opportunities be provided for qualified students to receive summer work in epidemiology at selected universities and governmental agencies (Recommendations 5-12, 5-13, and 5-14).

BACKGROUND DOCUMENTS

Document Number	*Author*	*Title*
EP-1	Hatch, T.	Non-Specific Contributions of Environment to Ill Health.

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Chapter 6

EPIDEMIOLOGIC ASPECTS OF CARCINOGENESIS

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EPIDEMIOLOGIC ASPECTS OF CARCINOGENESIS*

I. Introduction

Cancer causes over 300,000 deaths annually in the United States—about one-sixth of all deaths. The costs in direct care and treatment of cancer patients were estimated by the President's Commission on Heart Disease, Cancer and Stroke (DeBakey, 1964) as $1.2 billion annually. Adding estimated losses in earnings of the potential labor-force, the national cost rises to $8 billion, or 1.4 percent of the gross national product (1962 data). There is abundant evidence that the great majority of malignant neoplasms—probably over 90 percent of the total—are induced, maintained or promoted by specific environmental factors. Many of the known environmental causes of cancer are physical and chemical agents that directly concern the environmental health professions. Carcinogenesis must therefore be regarded as one of the most significant potential consequences of environmental contamination.

The subject of environmental carcinogenesis overlaps with the concerns of all of the Subtask Forces and Subcommittees, and all have made recommendations bearing on it. However, in view of its paramount significance, it seems useful to devote some attention to the problem *sui generis*. The particular emphasis of this discussion is on the study of environmental carcinogenesis *in man*, as distinct from the emphasis on experimental investigations in animals given by the Subcommittee on Carcinogenesis, Mutagenesis and Teratogenesis (Chapter 7).

As with other epidemiologic problems, there are two general approaches to clarification of the relationship between human cancer and the environment: (a) frequency of cancer is studied among people exposed to some agent which, on clinical, experimental, theoretical or intuitive grounds, is suspected of carcinogenic potential, and (b) frequency of suspected environmental exposures is studied in the histories of persons who develop cancer and of controls without cancer. In addition, studies of the distribution of cancer in the population and of variations in frequency between populations may help to suggest which cancers may be most fruitfully studied, as well as which environmental exposures should be examined.

II. Cancer Surveillance

For no disease are the routinely published data completely adequate, but those

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* This Chapter was prepared by Dr. Brian MacMahon.

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available for cancer are probably as good as for any other category of disease. The high case-fatality rate of most forms of cancer makes mortality data satisfactory for many purposes. In addition, there are incidence data from the Connecticut Cancer Registry and some 30 other population-based registries around the world. A first volume of data from these registries has been published by the International Union Against Cancer (Doll, *et al.*, 1966), and a second volume will be published in 1970. The National Cancer Institute has conducted two periodic surveys of cancer in selected metropolitan areas of the United States (Dorn and Cutler, 1959), and a third survey is now in progress. These sources, generally speaking, have provided an adequate base for a rather complete description of the demographic distribution of cancer.

In the last few years, considerable interest in cancer surveillance has focused on the identification of time-space clusters, particularly of leukemia. However, despite the reporting of a few striking episodes, statistical analyses indicate that, if any clustering at all is occurring beyond that which would arise by chance, it is quite rare and at a level of which the biologic interpretation is extremely problematic. Burkitt's lymphoma is the exception to this generalization. Clustering does appear to be significant in this tumor. In addition, the possibility of clustering of acute lymphoblastic leukemia in children under one year of age cannot be ruled out. While further investigation of these two diseases is needed, this is not sufficient to justify expansion of the cancer surveillance program as a whole.

III. Cancer and Occupation

The use of occupational and industrial groups in studies of environmental health has been stressed in various sections of the report. In relation to cancer specifically, occupational studies have served to identify many agents not previously known to be carcinogenic (soot and skin cancer, aromatic amines and bladder cancer, radon and lung cancer, etc.). Some of these agents are of practical concern only within the industry itself, but in other instances, for example in the case of asbestos and lung cancer, the agent may be one of considerable concern—present or future—to the population as a whole. In other instances, even when the agent is localized to specific occupations, the industrial experience may have a much broader application by providing opportunities for increasing understanding of the biology of cancer in man. For example, synergism in relation to cancer in man has been identified only with respect to the combined action of cigarette smoking and occupational exposure in causing cancer of the lung.

There is still much to be learned from the study of occupational cancers. The lung cancers of uranium miners and asbestos workers are likely to provide the most complete models of carcinogenesis in man and it is most important that as much information as possible be obtained from these numerically limited populations. One of the earliest identified occupational cancers was cancer of the bladder, and a number of the responsible chemical agents have been identified. Yet we still do not know the full range of industrial situations in which these agents are encountered in carcinogenic doses and we do not have any idea as to what proportion of the total bladder cancer problem can be attributed to occupational exposures.

It is also likely that many other occupational cancers remain to be identified as such. In comparison with other countries, the United States has very poor information on the relationship of either general or cause-specific mortality to occupation. The problems here—including the occupational mobility of the population and the inadequate correspondence of reporting of occupation in census reports and on death certificates—are considerable. However, at least one very useful report on the subject has been produced by the National Center for Health Statistics (Guralnick, 1963), and others should be encouraged. When hospital diagnoses become available for defined populations, there will be additional opportunities for studying the occupational distribution of patients with selected forms of cancer. The extensive hospital material of the Veterans Administration, which, as noted in the report of the Subcommittee on Epidemiology and Biometry (Chapter 5), can be linked to death reports through the resources of the National Academy of Sciences Follow-up Agency (DeBakey and Beebe, 1962), might also prove a particularly useful source of information.

> ***Recommendation 6–1:*** **Occupational carcinogenesis should be given high priority as a basis for selecting industrial groups for intensive investigation. The continuation of the on-going studies of lung cancer in uranium miners and asbestos workers should be given the highest possible priority. Cancer of the bladder deserves intensive investigation not only because of its position as an increasing public health problem, but also because research in this area may elucidate or explain synergistic effects and other aspects of human carcinogenesis.**
>
> ***Recommendation 6–2:*** **Further attention should be given to the identification of a patient's occupation in hospital records, death certificates, cancer registries and other sources of routine data. There is a need for exploratory studies to develop a simple questionnaire which will reveal significant occupational exposures and which might be incorporated into routine clinical histories in hospitals and other settings.**

IV. Geography and Cancer

Striking variations in cancer frequency are seen among different areas of the world. For example, areas have been identified where cancer of the esophagus is more than 100 times as frequent as in the United States. Even common tumors, such as cancer of the breast, colon and prostate, show variations between countries of 10- to 30-fold. Some situations have been identified where these variations are seen over quite short distances within the same country, as, for example, with esophageal cancer around the Caspian Sea. Studies of migrant populations, while still not as complete as could be desired, suggest that for the most part these variations must be attributed to characteristics of the local environment rather than of the genetic make-up of the inhabitants. No doubt some of the variations are due to differences in nutrition, clothing and other environmental factors not usually conceived as being within the realm of "environmental health", but there is also considerable concern that local soil characteristics and metallic and other chemical constituents of water and air may be of significance. To take even a disease of supposedly "known etiology", it is not known to what extent the extraordinarily high rate of lung cancer in Britain is due to an additive, or perhaps even synergistic, effect of air pollution over and above the known etiologic role of cigarette smoking.

Variations in cancer rates of the order seen on an international basis are, generally speaking, not seen within the United States—an expression, perhaps, of the relative uniformity of the man-made components of our environment. It would be wise to take advantage of the striking opportunities for identification of environmental factors in cancer that exist in other countries or in comparative studies between countries. A very strong case indeed can be made for the support of epidemiologic studies of environmental carcinogenesis in other countries, particularly in collaborative efforts with scientists in the United States.

> ***Recommendation 6–3:*** **Epidemiologic studies of environmental factors in cancer should exploit the marked geographic variations observed within and between countries. Modern statistical methods should be exploited to investigate the relationship between cancer rates by site (expecially perhaps, cancers of the digestive tract) and specific components of soil, water and air.**

V. Cancer in Children

If attention were to be focused on any one group of neoplasms of unknown cause, cancers of childhood, including childhood leukemia, probably deserve first priority. The incubation periods are clearly shorter than those of most tumors in adults, which should facilitate identification of the inducing agents. In addition, clinical associations between specific congenital malformations and certain childhood neoplasms suggest that some prenatal environmental factors may be common to both groups of diseases. The known greater susceptibility of rapidly growing tissue to carcinogens suggests on theoretical grounds that the child population should be watched particularly closely for evidence of the unintentional introduction of new environmental carcinogens.

> ***Recommendation 6–4:*** **Clinical, epidemiologic and cytogenetic research into the etiology of cancer in children should be maintained at a high level.**

VI. Cancer in Domestic Animals

There has been increased interest in recent years in the problem of cancer in domestic and agricultural animals. Living in more natural circumstances than laboratory animals, and sharing many of the features of man's own environment, these animals form an intermediate step in the process of extrapolating from animal to man. In addition, experimental work showing species variation in the effects of oncogenic viruses has raised the possibility of etiologic relationships between neoplasms in man and those in his closest animal associates. While this last possibility has not yet been demonstrated, preliminary results of attempts to register and investigate tumors in domestic animals have yielded interesting and potentially useful observations on the distribution of lymphomas and cancers of the breast and other organs.

Recommendation 6–5: **Studies of the distribution and etiology of tumors in domestic and agricultural animals deserve continued support.**

VII. Summary

It has been estimated that 90% of all malignant neoplasms are due to environmental factors. Many agents to which people are exposed at work have been shown to cause cancer and other occupational cancers probably remain to be identified. Further study of occupational cancer, particularly cancer of the lung in uranium miners and asbestos workers and cancer of the bladder in workers exposed to a number of chemicals, may provide an understanding of the mechanisms of carcinogenesis and is therefore recommended (Recommendation: 6–1). Improvement in occupational information in hospital records, in cancer registries and on death certificates would materially assist the identification of other occupational cancers. For this reason, the Subcommittee recommends exploratory studies to develop a simple questionnaire which will include such information and could be incorporated into routine clinical histories (Recommendation 6–2). The striking variation in cancer rates in different areas in the world provides a challenge and an opportunity to identify the environmental factors which must be responsible. International collaborative epidemiologic studies with United States scientists are strongly recommended (Recommendation 6–3). For many reasons, studies of cancer in childhood deserve special emphasis and research in this area should be maintained at a high level (Recommendation 6–4). Studies of the distribution of cancer in domestic and agricultural animals may yield information which would be relevant to understanding environmental causes of cancer in man (Recommendation 6–5).

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Chapter 7

CARCINOGENESIS, MUTAGENESIS, AND TERATOGENESIS

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CARCINOGENESIS, MUTAGENESIS, AND TERATOGENESIS*

I. Introduction

Those concerned with safeguarding man's health must assure that the benefits of new technologies and new products are attained with minimal risk to man's health and well-being. To accomplish this goal requires new approaches. Rather than depending on hope, luck and hindsight (as has often been the case up to now), more careful surveillance of the health of the population and more systematized testing of the safety of individual chemicals now in use, or proposed for future use, must be employed.

Among the potential effects from chemicals released to the environment, three are of particular concern. These are (1) carcinogenicity, (2) mutagenicity, and (3) teratogenicity. These three classes of effects share certain features: their insidious nature; a relatively long time lag between exposure and overt effect; the irreversible nature of the disease; the relatively great susceptibility of immature or developing tissue; the ability of etiologic factors, other than the one of interest, to produce the same endpoint (i.e., non-specificity of cause and effect); and the aggravation of effects from synergistic interactions of environmental agents. All these factors contribute to the necessary complexity of scientific investigations on cause and effect relationships. As a result, it is difficult to develop simple and reliable tests for evaluation of the products of new technologies and, in fact, new products are being introduced into our society faster than their safety can be ascertained.

The three previously cited classes of effects from chemicals released into the environment are further complicated by difficulties in defining or even estimating a tolerance level. One approach is to declare "no tolerance" for potentially hazardous agents. If on the other hand a given level is permitted, then one has to carefully weigh the risks of fatal, crippling or inheritable disease against the economic benefits of the proposed application.

On the basis of this situation, the Subcommittee makes the following general recommendations.

Recommendation 7–1: **Improved methods for the monitoring of data on cancer, malformations and genetic damage in human populations are needed.**

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* This chapter was prepared by a Subcommittee chaired by Dr. Hans L. Falk. Other people who participated in the preparation of this material included Drs. E. Cuyler Hammond, Marvin S. Legator, James G. Wilson, Gerald N. Wogan, and Arthur H. Wolff.

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(See recommendations of the Subcommittee on Epidemiology and Biometry, Chapter 5).

The research laboratory must work in a complementary fashion with investitions on human populations. Experimental studies should provide leads for epidemiologic inquiries and should elucidate cause-effect relationships inferred from epidemiologic findings.

***Recommendation** 7–2:* **Consideration should be given to systems for information collection, initial evaluation and retrieval of all research results (positive, negative or equivocal) on carcinogenesis, mutagenesis, and teratogenesis and other aspects of interference with reproduction.**

Difficulties in having negative or equivocal research data accepted for publication in professional journals or the reluctance of investigators to prepare formal reports on such data frequently deprive others from obtaining important and relevant information, thus leading to unnecessary duplication of efforts.

***Recommendation** 7–3:* **Experimentation concerned with comparative metabolism including storage, distribution and excretion of environmental chemicals in relevant species should be encouraged.**

It is well known that species differ considerably in their response to carcinogenic, teratogenic, and mutagenic agents because of characteristic differences in metabolic pathways or rates of reaction of detoxification. In order to interpret the biologic significance of different responses, data should be collected on such parameters as tissue distribution, storage, retention, rate of excretion, and enzyme patterns and kinetics, in species where differences in carcinogenic response have been noted. Wherever possible, such research should include at least one route of exposure which duplicates conditions generally encountered by man.

***Recommendation** 7–4:* **It is imperative that studies be conducted on the synergistic or antagonistic interactions between environmental carcinogens, mutagens, teratogens, and other agents (physical, chemical and biological).**

In most cases cancer in man appears to be the result of exposure to minute amounts of carcinogen with repeated exposure to promoting agents which reduce the latent period and bring out cancer within his lifetime. This concept has been clearly demonstrated in the laboratory.

In the sections to follow, specific research recommendations are given for each of the three potential effects of environmental chemicals.

II. Carcinogenesis

***Recommendation** 7–5:* **Since no presently available rapid-screening method is judged to be adequate for evaluating the carcinogenic activity of environmental agents, new approaches for rapid testing must be explored.**

Present procedures utilizing only *in vitro* systems, such as tissue culture, organ culture, and chemical interactions with macromolecules, are not considered adequate for bioassay purposes. Rapid test systems cannot produce unequivocal results that can be used to establish carcinogenic hazards until the results agree with paralled studies involving the intact animal.

Recommendation 7–6: **Conservatism is urged in exploring new animal species for carcinogenesis testing unless they appear to afford significant advantages over those currently used.**

The temptation to explore new and exotic species for carcinogenic studies is often great, but the considerable difficulties in reaching a base line for comparison (requiring years of study in genetics, toxicology, biochemistry, cytogenetics, parasitology, animal husbandry, etc.) militates against this exploration unless its advantages can be clearly established.

Recommendation 7–7: **Additional research should be performed to substantiate the relevance of the use of newborn rodents to the evaluation of carcinogenesis in man.**

The unusual sensitivity of newborn animals necessitates careful interpretation when animals at this age are used for bioassay procedures. Results partly due to toxicity leading to necrosis and regeneration often differ from those obtained by feeding the same chemical to weaned animals. Positive results obtained with the newborn may frequently be contradicted in experiments using the mature animal.

Recommendation 7–8: **The usefulness of multiple generation studies in rodents for carcinogenesis should be explored.**

Limited data suggest that exposure of parent animals to chemical agents may result in increased tumor susceptibility in subsequent unexposed generations. If confirmed, this phenomenon should be exploited.

Recommendation 7–9: **Use of pathogen-free animals maintained on semisynthetic diets should be considered for any long-term, carefully controlled study. Every effort should be made to avoid intentional or accidental contamination with pesticides, pesticide synergists, or disinfectants.**

Consideration of the use of pathogen-free animals is suggested because of their increased health and longevity as compared to conventional animals. It should be recognized, however, that pathogen-free animals do not represent an adequate comparison to normal conditions of man and that maintenance of such animals is difficult and often cumbersome.

Recommendation 7–10: **Rodent species (rats, mice and Syrian hamsters) should be the animals of choice for experiments of a screening nature or requiring large numbers of animals.**

Continued emphasis on rodent species is suggested since most comparative information has been derived from these species and their viral profiles, longevity, and susceptibility to diseases have been well established over the years (Berenblum, 1969).

Random-bred animals are thought by many scientists to represent the best choice for screening purposes; inbred strains may be more appropriate for other purposes.

Recommendation 7–11: **In assessing the carcinogenic potency of chemical compounds, more emphasis should be placed on inhalation as a route of exposure.**

Besides oral and epidermal application of environmental agents which are easily accomplished, the lungs are the most important organ of contact with environmental chemicals and need adequate consideration as a test system.

Recommendation 7–12: **Modulating factors in the host, including hormonal, immunologic, nutritional, and genetic parameters must be studied.**

During the long interval between exposure to a carcinogen and the overt appearance of cancer, many factors come into play which may enhance or suppress the development of cancer. Several factors are often simultaneously operative.

Recommendation 7–13: **Those responsible for the design of experiments in carcinogenesis should be aware of, and give careful consideration to, the possible contribution of viral agents as carcinogens or co-carcinogens.**

Murine viruses have been found to produce leukemia and other cancers in mice. Viruses obtained from species far removed from the murine host (i.e., from monkeys and cats) have induced leukemia and other cancers in rodent species. Activation of a "provirus" by ionizing radiation, producing leukemia in mice, suggests by analogy that activation of cancer viruses by certain chemicals may be a possibility.

It is therefore important to be aware of viral contamination as a complicating influence in chemical carcinogenesis. It is also important to explore the synergistic effects between non-oncogenic and oncogenic viruses as well as those between viruses and chemicals in carcinogenesis.

III. Mutagenesis

Recommendations 7–14: **The induction of mutations in man by environmental agents is sufficiently important to warrant intensive investigation. Efforts to improve existing techniques and to develop new ones for detecting mutagenic agents are urgently needed.**

The induction of detrimental mutations in a variety of biological systems attests to the importance of the problem at all phylogenetic levels. Since they are based on extrapolations from experimental data on lower forms of life, estimates on the induction of mutations in man can at best be only rough approximations (Auerbach, 1967). In the field of radiation mutagenesis, it is generally accepted that the dose-effect pattern for genetic damage in man is not remarkably different from that for other biological systems. It is likely that this concept is applicable as well for chemical mutagens. The perpetuation of genetic effects to future generations emphasizes the importance of the problem and the need to systematically evaluate known environmental contaminants for mutagenic activity (Crow, 1968). Methods are presently available in metazoans that will probably detect certain classes of chemical mutagens; however, a great deal of exploratory research is needed in method development in order to provide a better scientific basis for the quantitative assessment of environmental mutagens.

***Recommendation** 7–15:* **The Subcommittee recommends that judgments about mutagenic action in man should be made only after data from all the best available systems have been carefully assessed.**

In the last three to five years, a number of methods have been developed for evaluating mutagenic agents in relatively simple systems such as bacteriophages, microorganisms, drosophila, and cell cultures (Orgel, 1965). Particular note should be taken of the recently developed capability of scoring both forward and reverse mutations in cultured mammalian cells; however, one can seriously question if any greater significance can be placed on data obtained from cultured cells over that obtained from microorganisms.

The combined results of the following *in vivo* procedures would be helpful in evaluating mutagenic agents.

Host-Mediated Assay—This assay detects point mutations in microorganisms implanted into a mammalian host. In this procedure the mammal, during treatment with a potential chemical mutagen, is injected with an indicator microorganism in which mutation frequencies can be measured. The mutagen and the microorganism are always administered by different routes. After a specific time period, the microorganisms are recovered from the animal and the induction of mutants is determined. The comparison between the mutagenic action of the compound on the microorganism directly, and in the host-mediated assay, might indicate (a) how fast the host can detoxify the compound or (b) if the host forms mutagenic breakdown products during the metabolism of the compound, which come in contact with the microorganisms (Gabridge and Legator, 1969).

This is a quick, simple method for screening chemicals. One of the advantages of this procedure is its flexibility. A wide range of animal species, as well as numerous microbial indicators and possibly mammalian tissue culture cells, can be used.

Bacteria as well as cell cultures, while furnishing valuable information on the molecular mechanism for the induction of mutations by a specific chemical, should be considered only supportive to the mammalian studies in assessing environmental mutagenic hazards.

The Dominant Lethal Test—In this procedure, individual treated males are mated with successive groups of virgin females for a period up to 8 weeks and both preimplantation and early post-implantation deaths determined in mid-pregnancy. In this way the stage of spermatogenesis that was affected by the chemical mutagen can be determined, and one can exclude non-genetic systemic effects on the female (Bateman, 1966).

Chromosome Aberrations—Cytogenetic change in intact animals, especially at the level of germinal cells, is a selective, significant indicator of mutagenic effects. The specific types of chromosome aberration will determine the relevance of the data. Viable cells exhibiting exchange figures or single-chromatic breaks and other chromosomal abnormalities may be of great importance for transmittance of mutations to the progeny, while cells exhibiting fragmentation are usually non-viable and hence pose no genetic threat to future progeny. It is highly desirable to combine cytogenetic analysis with long-term experiments for carcinogenesis.

Biochemical Studies—In cultured mammalian cells, there is evidence that chemicals can induce biochemical mutants that are resistant to drugs. At this time there is no comparable report of induction of biochemical mutants in mammals. The possibility of detecting biochemical mutants and utilizing such a system for mutagenic screening purposes seems excellent. Another approach would be to screen for mutants on the basis of differences in the electrophoretic patterns of hemoglobins, enzymes and other proteins. Electrophoretic differences should be detectable in the heterozygote, i.e., the first generation (F_1), after the mutagenic treatment.

> ***Recommendation 7–16:*** **Attempts should be made to develop a more sensitive indicator for point mutations in mammals.**

In a population of animal cells, three levels of mutagenic activity can be determined: invisible genetic damage (i.e., point mutations), visible damage (i.e., detectable chromosome aberrations), and gross damage leading to cell death.

The region of point mutation is of the greatest concern for the transmission of inheritable changes, and agents that produce predominantly point mutations must be viewed as potentially the most hazardous type. The host-mediated assay and the detection of biochemical mutants can be used to evaluate point mutations, but development of new methods to determine point mutation in mammals represents a challenge for research. Limitations on the number of animals that can be handled, and the number of offspring per female, present some of the difficulties.

The specific locus test is an example of the type of procedure needed to determine point mutation in mammals. In this test, mouse coat colors and morphological markers (seven specific loci) are used to estimate both forward and reverse mutation rates. Treated wild-type males are mated to untreated female mice that are homozygous for the seven recessive genes. An estimate of the rate of induction of recessive mutations at the seven loci is calculated. This test provides a direct measure of recessive mutations in a mammal. Further development of this method (to include many more markers) and the development of new procedures to detect point mutations would be of great value (Russell, 1954).

> ***Recommendation 7–17:*** **In addition to evaluation of direct mutations, consideration should be given to chemicals that may interfere with normal genetic repair mechanisms.**

In microorganisms it can be demonstrated that errors in repair can lead to mutations. Certain chemicals, i.e., caffeine and acridine dyes, are known to impair normal genetic repair processes. In the presence of these chemicals, mutagenic agents such as mitomycin, aflatoxin, or 5-bromodeoxy uridine show increased mutagenic activity. Research is needed to elucidate and expand on the few known examples in microorganisms and cultured cells. The genetic repair mechanisms and the effects of compounds that alter repair mechanisms in metazoans need to be studied.

Recommendation 7–18: **Data on fetal deaths, sentinel phenotypes, chromosome abnormalities, and biochemical mutations should be collected to monitor human populations. (See also the recommendations of the Subcommittee on Epidemiology and Biometry, Chapter 5.)**

It would also be desirable to monitor stable human populations exposed to specific environmental factors to determine the fluctuation in mutation frequency over a given time interval.

IV. Teratogenesis

Recommendation 7–19: **The mammalian embryo has been shown to be most sensitive to teratogenic and embryolethal factors during the period of early organogenesis. For this reason, testing of potential environmental influences should be limited to this period or to other periods of suspected special sensitivity.**

Chronic or long repeated testing may reveal some teratogenic or embryolethal effect, but there is a demonstrated likelihood of obscuring or exaggerating effects on the embryo secondary to adaptive or pathologic changes in the maternal organism. Exposures for more than a few days have been shown capable of inducing the following types of changes in the maternal protective mechanisms:

1. Induction of hepatic catabolizing enzymes that may speed up metabolism of the test substance, thus tending to reduce effective dose;
2. Pathologic change in maternal liver or kidney of such degree as to reduce the metabolic or excretory function of these organs, with resulting increase in biologic half-life in maternal blood of the test substance;
3. Interference with such events in the reproductive process as conception, implantation, or continuation of pregnancy thus precluding observations on the conceptus.

Recommendation 7–20: **Attention should be focused on the possibility of developmental deviation induced at times other than at the accepted period of high sensitivity in the early embryo; that is, in the fetal period characterized by growth and functional maturation or even postnatally when the histogenesis and myelination of the central nervous system occur.**

The increasing recognition of developmental errors having a functional or biochemical basis (inborn errors of metabolism, mental deficiencies, etc.) suggests that environmental influences may act at later stages in development than in the early embryo when anatomical defects are known to be induced. Such late-acting influences would probably require the presence of chemicals in larger dosage and/or for a longer period than is the case with embryo-induced malformations, but such conditions are within the realm of possibility and should be sought.

Recommendation 7–21: **The factors and conditions responsible for establishing and maintaining concentration gradients of environmental chemicals across the placenta are urgently in need of investigation.**

The placenta has been shown not to be a barrier in any real sense because it probably admits to the embryo and fetus a portion of all substances present in maternal plasma except very large or highly charged molecules. Thus, the rate of placental transfer in both directions determines the concentration of a substance in the embryo. The resulting concentration gradient may be decisive in determining teratogenesis.

The placenta can, however, be an effective protective device if it transfers a chemical slowly enough to prevent a critical concentration from arising in the embryo. On the other hand, unidirectional transfer toward the embryo would permit a concentration build-up in the embryo of higher magnitude or longer duration than in the mother, thereby favoring embryotoxicity at low exposure.

Recommendation 7–22: **The development of metabolic competence to handle foreign substances in the embryo and fetus is a crucial subject about which little is known. Research in this subject area is urgently needed.**

At least some of the early embryo's high susceptibility to tetratogenic chemicals is attributable to its lack of an active catabolizing system; converselv the increasing resistance of the older embryo and the fetus may be partially dependent on the development of such a system.

Recommendation 7–23: **The Subcommittee urges that research be undertaken on new approaches to the elucidation of the mechanisms of teratogenesis.**

Information on the mechanisms of teratogenesis is at present very limited as far as mammals are concerned since it is almost entirely derived from comparative studies in sub-mammalian forms. Precise information is essential if potential teratogenic hazards are to be anticipated and avoided. Such information might also afford opportunities for prophylaxis.

Recommendation 7–24: **Research should be undertaken to determine the basis of species differences in teratogenic susceptibility so that the choice of test animals can be made with greater assurance of correct extrapolation to man.**

Wide divergence in teratogenic susceptibility is known to exist among the mammalian species used in testing (rodents, rabbits, and macaque monkeys). Thus all species are not equally useful in testing substances potentially hazardous to man The basis of species differences is assumed to be at least partly dependent on metabolic and adaptive differences in the maternal organisms (nature and extent of catabolic degradation, degree of protein binding, rates of excretion), but this remains to be substantiated. If metabolic patterns are shown to be the principal determinant of species differences in teratogenic response, teratogenic testing can be more confidently done in the pregnant animal that metabolized the test substance most like man.

Recommendation 7-25: **The Subcommittee strongly recommends the establishment of a registry of developmental deviations. Deviations should be included regardless of whether they are anatomic, biochemical, or physiologic in nature and of whether they are thought to be the result of genetic, environmental, or combinations of factors. (See recommendations made by the Subcommittee on Epidemiology and Biometry, Chapter 5.)**

Past attempts to collect comprehensive data on *all* types of developmental errors have been incomplete in one or another of the respects alluded to above. Furthermore, the critical matters of classification and nomenclature have not been satisfactorily resolved because representatives of all disciplines directly involved have never been brought together to integrate their particular interests and prejudices. The initial step, therefore, should be development of systems of classification and nomenclatures that are comprehensive and acceptable to pathologists, embryologists, and epidemiologists alike.

Recommendation 7-26: **The possible effects of environmental agents on such reproductive events as the maturation and transport of germ cells and fertilization and implantation are little known. The Subcommittee recommends an investigative effort in this area.**

These events have been shown to be vulnerable on exposure to a few outside influences and their critical position in the reproductive process requires that they be studied in relation to a broad range of environmental conditions, e.g., physical and chemical factors.

V. Summary

The Subcommittee focused special attention on those areas of research in carcinogenesis, mutagenesis, and teratogenesis where existing activity seemed inadequate to meet the urgent need for knowledge. In line with this approach, detailed recommendations are given for studies on the mechanisms of action of teratogens. Because similar studies in the areas of mutagenesis and carcinogenesis were believed to be well underway in many laboratories, the extent of recommendations in these areas is limited.

The basic goal of the recommendations was to facilitate the most suitable screening of environmental agents for their pathologic effects. Effort has been made to emphasize studies which will permit the greatest degree of extrapolation of the resulting data to man. Separate recommendations are given for carcinogenesis (Recommendation 7-5, 7-11 and 7-13), mutagenesis (Recommendations 7-14 and 7-15) and for teratogenesis (Recommendations 7-19, 7-20, 7-23 and 7-26). To make extrapolations potentially less tentative, recommendations are given for studies of metabolic pathways and modification of enzyme activities, as well as for comparative studies of the distribution, storage, and elimination of suspect chemicals (Recommendations 7–3, 7–16, 7–21 and 7–22). Included also are recommendations for the selection of animals for use in carcinogenesis and teratogenesis testing (Recommendations 7–6 through 7–10, and 7–24). Because the Subcommittee believes that the evaluation of modifying influences, particularly synergistic interactions, are in need of attention, concerted efforts are called for in these areas (Recommendations 7–4, 7–12, and 7–17).

Most of the recommendations focus on laboratory research. A few, however, deal with epidemiologic investigations, especially for those cases where a stable population is exposed to a specific environmental or occupational hazard or where toxic manifestations can readily be detected (Recommendations 7–1, 7–18, and 7–25).

Last but not least, the Subcommittee appeals to scientists to make negative or equivocal data on carcinogenesis, mutagenesis, and teratogenesis available in the published literature (Recommendation 7–2).

BACKGROUND DOCUMENTS

Document Number	*Author*	*Title*
TX2–1:I	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part I
TX2–1:II	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part II
TX2–1:III	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part III
TX2–1:IV	Falk, H. L.	A Review of Syn-, Co-, and Anti-carcinogenesis.
TX2–2	Wilson, J. G.	Environmental Hazards to the Reproductive Process.

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Chapter 8

TOXICOLOGY

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TOXICOLOGY*

I. Introduction

Despite the large investment of time and effort on research in toxicology, there are several areas that are relatively unstudied, particularly with respect to the needs of environmental health science. In some cases an area of research has received extensive support and is undergoing rapid expansion, but still contains certain small wildernesses which are particularly limiting. The Subcommittee on Toxicology directed its attention principally to areas where research was most urgently needed and/or where success was believed most likely. Among these areas were: (a) the problems of extrapolating results from animals to man, (b) the detection of early or relatively low levels of injury, and (c) approaches to the study of interactions of toxic agents to produce synergism or antagonism.

This report should be considered together with that of the Subcommittee on Carcinogenesis, Mutagenesis and Teratogenesis (Chapter 7). A separate report on the latter topics was deemed desirable by the Task Force, since the problems inherent in assessing carcinogenic, mutagenic, or teratogenic potential of any physical, chemical, or other toxic influences are not simple extensions of the general difficulties which are dealt with in estimating the pharmacologic or toxicologic properties of such agents. The problems of assessing carcinogenesis, etc., can differ both qualitatively and quantitatively from those encountered in routine toxicity evaluations.

II. Testing in Animals; Predictions

A. Multiple Species; the Use of Rodents in Toxicity Testing

The mission of NIEHS is heavily concerned with making determinations as to the toxicity of various substances in man, yet this determination cannot generally be made by the intentional toxication of people. Inferences must therefore be drawn from studies in animals and, ideally, one would wish to know, from the animal studies, the input of an agent necessary to attain some definable degree of noxious effect in man. Surprisingly, the science of toxicology has not been very successful in attaining this end. One major obstacle has been the lack of reliable human toxicity data with which the predictive value of the animal data might be assessed in retrospect. The only meaningful retrospective analysis, known to the Subcommittee, of the predictive value of animal toxicity data deals with drug toxicity (Litchfield, 1962). In this study the occurrence of toxic effects of drugs was more accurately predicted in tests with the dog than with the rat. Neither animal was outstandingly predictive, but toxic effects noted in both species were considerably more likely to be seen in man than those occurring in either of the two species alone.

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* This Chapter was prepared by a Subcommittee chaired by Dr. James R. Fouts. Other people who participated in the preparation of this material included Drs. Leon Golberg, Paul B. Hammond, Harold C. Hodge, Morris A. Lipton, Sheldon D. Murphy, and Herbert E. Stokinger.

Studies of the predictive value of animal testing for human toxicology are needed. These studies should be specifically directed toward comparisons of toxicity in rodent and non-rodent species so as to determine whether there is anything unique about rodents as test animals. Data concerning the toxicity of the test compound in humans would be needed so that each species could be compared with man. Toxicities should be compared in terms of concentration of the toxic agent at or as near as possible to the site of damage. A systematic study of several species is needed before answers can be provided as to whether multiple species are better than one or two species in predicting human toxicity. Careful attention is needed to routes of administration and doses (dose ranges and duration of treatment). The key to these studies is the systematic comparison of several species (both rodent and non-rodent) with man using several toxic materials and/or drugs.

> ***Recommendation 8–1:*** **Comparisons of toxicity of several toxic agents should be made in rodent and non-rodent species, and in multiple versus one or two species. Careful correlation with toxicity found in man should be made.**

B. Development of Pre-Clinical Sensors of Toxicity

For most suspected environmental toxic agents, the validity of animal data for man cannot be ascertained because ethical considerations limit the intentional intoxication of human subjects. It therefore becomes important to identify in animals certain manifestations occurring reproducibly at exposure levels well below those causing overt signs of toxicity. These "early warning" signs, when applied to man, could serve as end points from which toxic levels might be inferred. Furthermore, "pre-clinical sensors" are often useful in control or surveillance programs, as in the case of delta-aminolevulinic acid excretion in relation to lead exposure.

> ***Recommendation 8–2:*** **"Pre-clinical" sensors of toxicity, i.e., systems which will show measurable changes at doses of toxic agents far below toxic levels, should be developed. Such sensitive systems must be found so that the very early stages of adverse effects can be detected. To be effective these "early warning systems" must be transposable from animals to man.**

C. Selection of Appropriate Experimental Animals

1. Species and Strains

The selection of a species of animal for study is not generally limited by availability or by any firm scientific guidelines as to what species most accurately mimics man. Practical considerations of cost, size, and quality are dominant in the absence of more sophisticated criteria. The rat and the mouse are most widely used in biologic research and have been for many years. Their desirability can be justified in many ways, not the least of which is the extensive information available concerning their proper husbandry, physiology, and pathology (see examples cited by Green, 1966; Brues and Sacher, 1965).

The decision as to whether inbred or random-bred strains are most desirable may be determined by the objectives of the proposed study. When little or nothing is known concerning the possible toxicity of an agent, optimal randomness providing the largest possible genetic variation may be desirable. It is a common experience among toxicologists to find large variations in susceptibility within a given strain procured from two different animal suppliers, or even from the same supplier at different times; the likelihood of never finding a toxic effect characteristic of the species seems great when testing is restricted to the genetic pool of one or even of several inbred strains. On the other hand, in-depth studies of mechanisms of toxicity may best be done using inbred strains, since it would appear that greater reproducibility of the results from one experiment to the next would be assured. The selection of an inbred strain, however, does not always assure low variability in response. In fact, inbred strains can be more variable in their responses to environmental stresses than are F_1 crosses (Biggers, 1958). Inbred strains may be selected for special characteristics appropriate to the experimental design. At least this can be done in the case of the mouse and to some extent the rat and hamster. Biochemical and morphologic oddities among inbred strains of mice are numerous and diverse (Meier, 1963).

> ***Recommendation 8–3:*** **It is recommended that highly inbred strains of animal species other than mice be developed. Of particular interest would be the ready availability of inbred strains of rats, rabbits, and non-rodents. Also needed are truly random-bred or "mongrel" strains of such common laboratory species. Both highly inbred and "mongrel" strains should be used in the thorough study of a given toxic material, drug, or environmental hazard. A systematic study should be made of whether mongrel or genetically pure animal strains are better for routine toxicity testing.**

2. Species Variability in Metabolism of Toxic Chemicals as It May Affect Toxic Actions

Patterns of biotransformation vary from species to species. Man may metabolize a chemical (e.g., beta-naphthylamine to alpha-hydroxy-beta-napthylamine) to form a carcinogenic product; the dog may do the same and like the man may develop a bladder cancer, whereas the rabbit may metabolize the chemical in another manner which produces a non-carcinogenic product. Therefore, the rabbit may not be a suitable animal species for predicting the safety or hazard of certain such molecules for man.

It is suggested that, where possible, metabolic studies in man precede extensive toxicity testing in animals so that a species can be selected with a metabolic pattern similar both qualitatively and quantitatively to that in man. This metabolic matching may be particularly important prior to chronic toxicity testing.

If none of the readily available laboratory or domestic animals uses a pathway of biotransformation for a given chemical like that in man, a systematic search in exotic species and strains might be conducted until an appropriate animal model has been discovered.

There may, however, be some basis for studies on species which differ from man in foreign compound metabolism for purposes of elucidating basic mechanisms. Examples of using information about comparative metabolism, obtained in species differing from man, in order to gain greater understanding of the mechanisms involved in carcinogenesis by aromatic amines, are summarized in the review by Weisburger and Weisburger (1968).

Recommendation 8–4: **A high priority should be given to the search for animal models of biotransformations that closely match those in man.**

D. Duration of Toxicity Tests

The earliest biologic evaluation of a new chemical form is often an acute toxicity test; finding the LD_{50} in mice or rats and/or the approximate lethal dose in rabbits, cats, dogs, or monkeys usually suffices. If the chemical is technologically promising, a relatively brief study is conducted in which its effects are observed over periods of 1 to 3 or more months of daily repeated doses frequently given by mixing the chemical at several concentrations in the diets of rats or dogs.

These results may justify the cautious dosing of human volunteers to obtain evidence of the metabolic transformations of the molecule in man (and perhaps of certain minor pharmacologic or toxic effects). Before extensive therapeutic studies of the efficacy and side effects of a candidate drug are begun, more intensive and prolonged animal toxicity tests are entered upon.

The chronic toxicity tests usually follow a simple pattern; 2-year (lifespan) studies in rats, and 1 to 2-year studies in dogs. The program of observations is generally based on the known or predictable properties of the chemical. Other species are occasionally included or substituted for rats or dogs. The selection of a species with a pattern of metabolic change similar to that in man is a laudable and perhaps a necessary improvement in the plan now commonly followed (see previous section).

Prolonged human exposure as a test procedure poses many difficulties. If the doses are substantial, the hazard may be unacceptable; if the exposures are unavoidable (industrial personnel, e.g.), the minuteness of the dose and the irregular and often unmeasured intake often defeat the purpose of the study (e.g., to find a dependably-tolerated dose).

For the present, animal tests seem to be the best, and often the only justifiable procedure for detecting systemic toxic effects. There is little chance of major modification of current practices without substantial new data justifying such change.

Lengthy chronic tests are used: (a) to identify carcinogenic potential, (b) to detect irreversible injuries that reduce life span, (c) to discover other cumulative effects, or (d) to explore the changes under exotic conditions such as prolonged submarine travel, existence in the sea lab at high environmental pressures, or lengthy space flights at reduced pressures. A psychological advantage to the investigator or to the administrator setting tolerance limits for prolonged human exposures is the often intuitive, sometimes illogical, but comforting reliance on lifespan exposures in some animal (e.g., the rat) when a substance is proposed for ingestion regularly over a major part of the lifespan of humans. The disadvantages are the space, the manpower and the funds preempted by a chronic study, and therefore unavailable for the examination of other compounds.

The problem is to assess the benefit gained from tests prolonged past, for example, one year. The pressures are great; the total facilities in the country for toxicologic testing are so limited that the choice of a shorter period, e.g., one year or less, if defensible, would be eagerly made. The lack of solid evidence to support this choice is a major deterrent. Many toxicologists share the opinion that treatments of six months or twelve months at the longest, with exaggerated doses, should provide evidence of almost any toxic effect except carcinogenesis. Only one published comparison of the effects discernible in short-term tests with those of two-year tests appears to be available (Weil and McCollister, 1963). Toxicity data of 33 different materials were compared. Certain criteria were regularly sensitive, others usually not; in general, the 90-day, no-effect level was almost as useful for tolerance estimation as the no-effect level found in the 2-year rat, or 1-year dog feeding studies.

The Food and Drug Administration (FDA) has what is probably the largest file of chronic toxicity tests extant. A staff toxicologist of the FDA (or the NIEHS) could properly be given access to this confidentially held material. The comparisons could be coded in such a way as to reveal the comparative findings (short-term, versus 1 to 2 years, versus lifespan test durations) without violating the confidential aspect of the data (e.g., the nature of the substances.)

> ***Recommendation 8–5:*** **That a staff toxicologist with suitable qualifications review the chronic toxicity studies in the files of the FDA to ascertain whether the qualitative and quantitative effects observed in the period up to one year differ from those observed using test durations significantly longer.**

III. Detection and Evaluation of Toxicity

A. Use of Multiple-Sequential and Integrated Systems to Determine Organ Function

Many of the organ function tests currently used to detect toxic effects of exposure to poisons, drugs, or pollutants suffer from the disadvantages that they do not point to the specific organ damaged, become abnormal only after massive doses of toxic agent, are abnormal only for short periods after "poisoning" or exposure, or give false negative values if the damage is slow to occur. Better function tests may result from studies which measure several steps in a sequence of reactions affected by the toxic agent. Thus, an effect on the liver's ability to detoxify foreign compounds might be studied by measuring (a) the actual toxic effect or blood levels of several other chemicals in the treated animal, as well as, (b) liver cytochrome P–450, (c) the microsomal drug-metabolizing enzyme activity using several substrates, (d) the activity of delta-aminolevulinic acid synthetase, and (e) the morphologic correlates of any change in enzyme activity (e.g., the amount and arrangement of liver cell smooth endoplasmic reticulum using the electron microscope). In order to be most reliable such multiple analyses should be possible on the tissues and body fluids, and should be compared with conventional function tests to establish advantages and disadvantages. Organ functions should be assessed in the living organism as well as *in vitro*.

Such analyses of multiple-integrated systems should be automated if at all possible. One aspect of automation of function tests which should be mentioned is that requirements for precision in such tests may be different and often greater than for clinical purposes in man. Species can also differ markedly in ranges of "normal" values of function. These differences can make a function test unusable in certain cases. Thus, serum alkaline phosphatase can be used as a test of certain liver functions in dogs (since hepatotoxicity results in marked increases from normally low values). However, this test is not useful in the Rhesus monkey since normal serum phosphatase values are very high in this species, and hepatotoxins do not induce much change in such already high serum enzyme activities. Properly applied automation of function tests is, however, absolutely essential to their widespread use, or to a reasonably quick decision about the merits of new function tests, since only in this way can enough test compounds and enough species be examined.

Recommendation 8–6: **It is recommended that sequential, integrated systems to detect early toxic changes be developed. The overall product of such a sequence of reactions may not alter in amount whereas each of several steps leading to that product may change greatly (increased steps balanced by decreased steps). On the other hand, a series of small damages may add up to a serious defect. Such systems should be measured in tissues and body fluids.**

Automated procedures should be evolved for the performance of tests chosen to study sequential, integrated systems. Only when these tests are automated can they be performed:

(i) Often enough;
(ii) All in the same tissue sample;
(iii) With a high degree of reproducibility and accuracy.

B. *The Importance of Organ Enlargement*

Organ enlargement (increase in mass and/or volume) is a frequent result of exposure to foreign compounds, drugs, or toxic agents (Smyth, *et al.*, 1952; Weil and McCollister, 1963). For example, in the case of liver, the increase in weight might be caused in any of at least three ways, only one of which may be injurious by some definitions (Golberg, 1966). A condition leading to liver enlargement of a "benign" sort may, if prolonged, lead to more serious consequences and evidence acceptable as indicating hepatotoxicity. This seems to occur in rats with continued exposure to dieldrin (Hutterer, *et al.*, 1968).

Bases for decisions about whether enlargement of organs is a sign of toxicity are not agreed upon. This problem could be approached somewhat more easily if the mechanisms of enlargement were better understood. Since these mechanisms are unlikely to be known very soon, whereas the problem is immediate and urgent, new information is needed. One possibility is to measure functions of the enlarged organ. Several functions of the organ should be studied, since some of these may remain normal while others are enhanced or depressed. These function tests should be repeated at various times during which the organ is enlarged (due to exposure to pollutants, postulated hazards, etc.), so as to determine if an initially innocuous effect becomes harmful when prolonged. These function tests should measure organ function in the living animal. Function tests should also be performed under conditions of loading, as well as under normal conditions, since a decrement in physiologic reserve of an organ may not be detected unless maximum functional demands are made.

***Recommendation** 8–7:* **Organ enlargement should be assessed in terms of whether this is a toxic sign. Several procedures to estimate the function of the enlarged organ should be used. An enlarged organ that adequately performs most vital functions especially when maximal demands are placed on it, could be viewed with less alarm than one where capacity, e.g., to detoxify, excrete, or synthesize protein, is decreased.**

C. *Morphologic-Physiologic Correlations of Cell Injury*

Too often morphologic change is the single most important, or even the only available, indication of tissue damage resulting from exposure of animals or man to poisons, pollutants, or new drugs. This situation is unlikely to change without determined and strenuous efforts showing the advantage of correlating morphology with chemical, biochemical, histochemical, autoradiographic, etc. studies. This correlative approach should be applied in several representative cases (using chemicals of known toxic effects) and with several species of animals in the same laboratory where the newer organ function tests mentioned at the beginning of this section are being developed. When thus validated, this approach may gain wider acceptance in testing unknown or postulated toxic agents.

It seems particularly important to note that certain types of morphologic studies should be applied only after other tests have indicated changes in cell function. An outstanding example of such necessity for restraint exists in the case of electron microscopy. This powerful methodology should be reserved for use in circumstances where other, and preferably several other, tests or approaches have indicated changes from normal functions which might be reflected in ultrastructural alterations. Such indicators could be marked changes in activity of an enzyme known to be localized in a specific subcellular organelle, or indications from light microsocopy of structural changes.

> ***Recommendation 8–8:*** **Morphologic studies used in assessing drug or chemical toxicity should be more closely correlated with function changes, enzyme assays, histochemistry, radioautography, and electron microscopic studies. Routine electron microscopic studies of tissue from treated animals or man is probably a waste of time. Electron microscopy should probably be used to better understand changes which can first be detected by light microscopy, histochemistry, or enzyme assays. The sum total of all investigations should allow assessment of most membrane and organelle functions of cells from treated versus control animals or man (by biopsy). The emphasis here should be on the planned choice of test systems and the integration and correlation of these studies to reach the goal of assessing cell function as it is affected by the poison or drug.**

D. *Behavioral Tests as Sensitive Indices of Toxicity*

A primary function of the nervous system is the sensing of stimuli, the processing and organization of these as information, and the execution of appropriate behavioral responses. The perception of noxious environmental stimuli by the sensory nervous system results in central nervous system activity with consequences on visceral and endocrine functions, motor activity, and mental processes such as emotional states and cognitive functions. Such alterations in homeostasis affect interpersonal relations, decision making and judgments.

It might then be expected that a prominent and promising area of active investigation in pharmacology and toxicology would be in the area of behavior. Unfortunately, it is not. Behavioral pharmacology is a new discipline which has been reviewed only four times in the Annual Review of Pharmacology. The most recent review in that series is by Weiss and Laties (1969). The first textbook of Behavioral Pharmacology by Thompson and Schuster was published in 1968. A new journal entitled *Behavioral Pharmacology* will appear this year, even though subjects in this area have appeared in the more traditional journals of pharmacology in the past decade.

Until recently, the only noted behavioral effects of drugs were of the crudest types. Gross disorders of perception, consciousness or coordination were the primary types of behavior recorded. The advent of psychotropic drugs and the recognition that agents exist which affect primarily mood, thinking, and behavior, has led simultaneously to a search for adequate methods for measuring such parameters in man and their analogues in other animals. Methods now exist for quantifying, in man, behavioral functions like mood, learning ability, memory capacity, concentration, etc. In addition to such formal psychologic tests, experienced clinicians are able to acquire significent information on man in relation to life style, relations to other people, and motivations. There are also useful psycho-physiologic tests for arousal, vigilance, stress, anxiety, etc. These tests and methods are currently used primarily for assessing degrees of psychologic disability in the variety of clinical syndromes which come to the attention of the psychiatrist. They are also used to test the effects of psychotropic drugs upon these conditions. Presumably they could be used just as effectively to study the effects of noxious environmental stimuli upon behavior, but relatively little work of this type has been done. To illustrate their potential utility the following example might be used. The most disabling symptoms of chronic carbon disulphide poisoning include irritability, depression, outbursts of violence, and strikingly evident personality disorders. Such changes apparently occur before significant somatic changes can be demonstrated. Similarly, the studies of Beard and Wertheim, 1967, have demonstrated a diminution of time sense in humans exposed to 50 ppm of carbon monoxide for as little as 90 minutes. Further exploitation of complex behavioral tasks, related when possible to the requirements of the job, in the presence of suspected noxious environments, would seem to offer promise as sensitive and relevant indicators of environmental toxicity. Such behavioral studies might be done directly on man when decrements are suspected. They almost certainly should be done when data from animal experiments or other sources indicate that the environmental agent in question passes the blood brain barrier and can be found, or perhaps even concentrated, in the brain.

In cases when naturally occurring experiments are not available, and ethical considerations limit active experimentation with humans, recourse must be taken to animal experimentation. Here, too, newer techniques are being developed which permit sensitive bioassays which may be quite relevant to human problems. Such techniques are largely dependent on the developments of either classical Pavlovian or operant conditioning techniques. In the former, which are popular in Europe and especially Russia, an animal which spontaneously responds to an unconditioned stimulus (e.g., salivation at the sight of meat) is trained to respond to an indifferent stimulus (a green light) by presenting it in temporal association with the unconditioned stimulus. After a time he will respond to the second or conditioned stimulus. The effects of a variety of agents at different concentrations can then be tested in terms of their capacity to alter the response to the conditioned stimulus. In operant conditioning, by contrast, an animal has a genetic repertoire of behaviors which he exhibits spontaneously. Experimental conditions are then designed to select the behavior which is desired by reinforcing it with a reward. In this fashion animals can be trained readily to perform what superficially seem to be fantastic tasks. When animals are so trained, the effect of drugs or toxic agents can be tested to determine the degree to which they disrupt or alter the performance. As illustrative cases, Armstrong, *et al.* (1963) studied the effects of mercury vapor on behavior of trained pigeons and were able to produce reversible changes in behavior before other types of overt pathology could be detected, and Beard and Wertheim (1967) were able to detect the effects of 10 minutes of exposure to 100 ppm of CO in rats trained to work on a spaced-responding reinforcement schedule. The imaginative use of these types of technique has been extremely effective in the study and development of psychotropic drugs, and in elucidating their mechanisms of action. They could be equally useful in the study of environmental hazards. With such techniques alterations in perceptual acuity and discrimination and phenomena such as vigilance, distractability, emotionality, and motivation might be studied.

The area of developmental psychopharmacology also warrants attention in relation to environmental hazards. Recent research has demonstrated that there are critical periods in which behavior can be permanently shaped (Glass, 1968). The administration of one dose of testosterone, for example, to 3 to 5 day old female rats, will alter sexual behavior for life. Similar changes in aggressive behavior can also be induced. In man, intrauterine exposures to aberrant endocrine concentrations can affect growth and maturation of the nervous system. After birth, protein deficiency during critical periods of growth has been shown to alter central nervous system maturation and intelligence. Stimulus deprivation at critical periods in the developing human also leads to later functional deficiencies. It seems reasonable to expect that exposure to environmental toxins at critical periods might do the same, though data are lacking. The expression of some genetic illnesses (e.g., phenylketonuria and galactosemia) can be prevented by elimination of nutrients toxic to this genetically-unique organism during critical periods of development. When more adequate methods are available for testing animal "intelligence", including learning capacity and memory, it should be possible to learn more about toxic influences upon the development of the higher mental functions. Such information should be relevant to man.

Still another area requiring research and wider recognition is that of drug-milieu interaction. It is well known among clinicians that many, if not most, drug effects depend upon the setting in which the drug is given. This is true not only for therapeutic agents, but especially for toxic agents which affect behavior. For example, the effects of an agent like LSD–25 may vary from panic, to amusement, to a religious mystical experience, depending upon the setting in which the drug is given. In lower animals, e.g., mice, the toxicity of stimulating drugs like amphetamines is strikingly affected by whether the mice are housed alone or aggregated. One may readily imagine that acute and perhaps even chronic effects of environmental agents or pollutants will also depend upon physical, psychological, and social aspects of the environment in which the exposure takes place.

The reader is referred to the report of the Subcommittee on Social and Behavioral Sciences (Chapter 9) for further discussion of the interactions of behavior and environment.

Recommendation 8–9: **Toxic features of the physical environment have been shown to have consequences upon complex behavior in both animals and man. Therefore behavioral scientists should be increasingly encouraged to participate in environmental research and the NIEHS should consider establishing a unit concerned with behavioral pharmacology and toxicology.**

IV. Drug and Foreign Chemical Metabolism

A. Species Differences in Enzyme Induction or Inhibition

The rate of metabolism of a drug or chemical can markedly affect its duration or intensity of action. Enzymes in the liver which metabolize foreign compounds (drugs or poisons) can be altered in amount or activity by previous exposure to a number of materials found in all parts of our environment—including drugs pesticides, solvents, and atmospheric pollutants such as benzpyrene. An animal or man with altered ability to metabolize or detoxify materials to which he is exposed (purposefully or not) may react quite abnormally to these exposures. Despite the intensive and extensive research in "drug metabolism" in many laboratories, there remains a need for a systematic study of how various animal species and man react to various materials shown to affect enzymes which metabolize foreign compounds (either to stimulate or inhibit these enzymes). The purpose is to gain knowledge about which species resemble man in their foreign compound metabolizing or detoxifying systems' response to previous exposure to inducers and inhibitors which are now widely used, or to which many people are exposed. It is known that stimulation of liver metabolism of foreign compounds can be affected by the dose, route and duration of administration, or exposure to the inducer. However, there is still need for a planned examination of each of these and other parameters (e.g., dose, duration of dose, route of administration, age of animal, health and/or diet, or environment of animal) in several species of animals for several of the more important inducers. Comparison of animal responses with responses in man should be made whenever possible, using cases of accidental poisoning in man with inducers such as insecticides, or barbiturates, or chronic exposures to polycyclic hydrocarbons (e.g., smokers vs. non-smokers). The pollutants of most interest at present appear to be the chlorinated insecticides and especially DDT (since DDT does not affect biotransformation mechanisms in all species), the polycyclic hydrocarbons and especially benzpyrene (again, since BP does not affect biotransformations in all species), and the barbiturates (because they are most widely studied and and will serve as reference). The species of most interest appear to be mice, rats, dogs, rabbits, and Rhesus and squirrel monkeys.

Recommendation 8–10: **A planned, systematic study should be undertaken of differences in species responses to inducers and inhibitors of the metabolism of drugs and foreign chemicals.**

B. *Rates of Metabolism of Foreign Compounds in Man*

Currently, the biologic half-life of a test substance is most commonly used to estimate the activity of detoxifying or metabolizing systems in man. One measures the rate of decline of plasma concentrations of "markers" like phenylbutazone, warfarin, aminopyrine, or antipyrine. This rate of decline is thought to be a function of metabolism and to change when metabolism or detoxification is affected or changed by inhibitors or stimulators of enzymes, e.g., insecticides.

Many of these test drugs are relatively toxic, e.g., phenylbutazone and aminopyrine, or are highly protein-bound, e.g., warfarin, so that their half-life is also determined by plasma protein binding. In order to know more about how animals and man compare, better techniques are needed to assess the activity of detoxifying or metabolizing systems in man. Better marker or test drugs are needed so that estimates can be made using urine or blood samples, and markers are needed for both oxidative and non-oxidative metabolic pathways. Foreign chemical metabolism needs to be studied in non-hepatic tissues as well as hepatic tissue.

There is a possibility that hepatic steriod metabolism, drug metabolism, and foreign compound metabolism are catalyzed by the same enzyme systems. Chemicals which stimulate the hepatic metabolism of steroids often enhance the urinary excretion of 6-hydroxycortisol both in animals and man. This product (6–HO–cortisol) is easy to measure and urine samples can be obtained easily and repeatedly. The usefulness of this marker should be established in terms of several species, several inducers and detoxifying systems.

> ***Recommendation 8–11:* Better estimates of the rate of metabolism of foreign compounds are needed for man. These better methods should be applicable to readily accessible tissues and body fluids which can be sampled repeatedly.**

V. Use of Model Disease States

The major diseases to which environmental pollutants are suspected contributors—cardiovascular and coronary heart disease, emphysema, bronchitis, cancer and aging—and which account for a great part of the morbidity and mortality in the U. S. population are diseases of multiple causation. In this framework, environmental pollutants are suspected of furnishing (with a few recognized exceptions) only contributing insults to a host already stressed by a number of environmental and host-related factors, each of the factors exerting a more or less prominent part in either the development of a particular disease or in the aggravation of existing disease (Stokinger, 1969).

Among the more important contributing factors are the following:

A. *Physical Factors in the Environment—Cold, Heat, Humidity and Noise*

Baetjer, *et al.* (1956, 1960, 1969) have shown enhanced toxicity of lead, antimony, and parathion at elevated temperatures, and Keplinger, *et al.* (1959)

have shown greatly altered toxicities of more than 50 substances at temperatures both above and below normal; the direction of the effect at cold temperatures depended upon whether the substance was a depressant or stimulator of the central nervous system. Noise as a form of stress can be of serious proportions; rat colonies have died from exposure to noise from jackhammers and concrete drills, and biochemical changes (blood glutathione) have occurred after a few minutes' exposure to noise of 100 decibels.

B. Sociologic Factors—Crowding and Irritations of Urban Dwelling, Smoking, and Abnormal Eating and Drinking Habits

Selikoff, *et al.* (1968) have found a three-fold greater risk of acquiring cancer among asbestos workers who were cigarette smokers than among asbestos workers who did not smoke. Micronutrient deficiency states, resulting from abnormal eating and drinking habits, have been suggested as playing a determinant role in influencing the onset of diabetes and atherosclerosis (Mertz, 1969).

C. Host-related Factors—Predisposition by Reason of Preexisting Disease, Pregnancy, Heredity or Concomitant Pollution Exposure

Bronchitis is believed to be initiated and aggravated by respiratory irritants, overlaid on an already-infected respiratory tract. The stress of pregnancy predisposes women previously exposed to beryllium to berylliosis (Stokinger, 1966). The familial form of pulmonary emphysema may be expressed in individuals with the hereditary abnormality of serum antitrypsin deficiency following exposure to respiratory irritants (Eriksson, 1965). Numerous experimental examples of synergism resulting from the interaction of chemical pollutants and microbial agents (infection) have been documented (Ehrlich, 1966; Coffin and Blommer, 1967; Stokinger and Coffin, 1968).

Physiologic age is recognized as a significant determinant in responses to environmental stressors of all types, be they physical or sociologic factors or environmental pollutants; susceptibility to environmental stress is greatest in the aged and the newborn.

In recognition of the above contributing factors, selection of animals for environmental health investigations should be tailored to simulate those aspects or conditions in the human population that are related to the disease process under study. A significant part of the simulation is the development and use of animal models of human diseases. A large number of mammalian and avian models of diseases in man have been listed and discussed by Frenkel (1969).

Recommendation 8–12: **It is recommended that greater use be made of "stressed" animals in research in environmental health. Such "stressed" animals could include the very young and old as well as those with model diseases (hypothyroidism, diabetes, etc.)**

VI. Interactions to Produce Synergism or Antagonism

A. Time and Dose-Response Relationships

Classicially, studies of synergism and antagonism have dealt with simultaneous exposures to combinations of chemicals, or exposures separated by brief intervals. It is now apparent that interactions are frequently best demonstrated when the intervals between exposures are separated by several hours or days. For example, potentiation of the toxicity of the insecticide malathion is greater when it is given several hours after pretreatment with certain other organophosphate insecticides, than when these are given simultaneously (DuBois, 1969; Casida, 1963). The protection by aldrin against poisoning by several organophosphate insecticides is not manifest until several days after its administration (Triolo and Coon, 1966).

One chemical may competitively inhibit the metabolism of another when they are given close in time, but may induce increased rates of metabolism when the interval is prolonged (Mannering, 1968). Tests for interaction should therefore be performed at a series of intervals between exposures.

Similarly, the toxicity of one compound in relation to another should be investigated by varying doses of each against a constant dose of the other. If toxic interactions occur at doses of either chemical which are appreciably below the threshold dose for the usual toxic effect of either chemical when given alone, or at a dose which is near the probable use level, the interaction should be thoroughly investigated. This approach should also apply to superimposing acute administration of one compound on the chronic administration of another, and will permit quantitative evaluation of threshold doses for both the potentiator and potentiated compound (Hewlett, 1960).

The prediction of interactions or the choice of pairs of toxic agents for study of possible interactions has usually been difficult to make. As pointed out by Laurence (1964), many clinically-observed toxic interactions might have been prevented if existing pharmacologic information had been fully used. Principles concerning competition for sites and mechanisms of action, and competition for sites and mechanisms of inactivation, storage and excretion of chemials, might be used to guide the design of a computer-directed program for prediction of interactions. In addition to such basic pharmacologic and biochemical data, input to the computer should include physical-chemical data, probable size of human populations that will be exposed, and other information relating to the exposure or use patterns and doses. Particularly, this should include input of data on pesticides, polycyclic hydrocarbons, food additives and frequently-used therapeutic chemicals. Initially such a computerized program should be tested with data on a few combinations of chemicals which have already been well-characterized for interactions experimentally. If it appears successful from these initial studies, the program might be useful for compiling priority lists of combinations of chemicals which should be investigated for interactions in experimental animals. As a minimum return, this system would be useful for data retrieval.

***Recommendation 8–13:* Toxic interactions should be thoroughly characterized in terms of their time and dose-response relationships. Attempts should be made to use computer programs to predict combina-**

tions of chemicals or toxic agents which are most likely to lead to adverse interactions.

B. Tests of Interactions, in vivo *and* in vitro

Measurements of inhibition or stimulation of enzymes metabolizing foreign chemicals is one useful mechanistic approach for screening chemicals for possible interactions (DuBois, 1969), but for quantitative evaluation of interactions it is important that correlations be made with toxicity tests in intact animals. Multiple enzymes, both detoxifying and activating, may be affected (Murphy, 1969). Whether synergism or antagonism occurs may depend upon the relative degree of stimulation or inhibition of two or more different enzymes which metabolize the same compound to either more or less toxic metabolites. Competition for binding sites as a possible mechanism for interactions has received relatively little attention, but recent evidence indicates that this mechanism can contribute to synergism of therapeutic chemicals (NIH Report, pages 94–98, 1968) and certain organophosphate insecticides (Lauwerys and Murphy, 1969). Additionally, competition for storage sites, or altered rates of metabolism which affect storage, have been noted in feeding studies of chlorinated hydrocarbon insecticides (Deichmann, *et al.*, 1969; Street, 1969).

> ***Recommendation 8–14:*** **It is recommended that greater effort be devoted to determining the quantitative relationships between effects of chemicals on enzymes that metabolize other foreign chemicals and the effective doses of these chemicals in intact animals. Other modes of inactivation such as protein binding, storage and excretion should also be considered.**

C. Acute Versus Chronic Interactions

Most current evidence of toxic interactions is based on acute responses. For example, certain aerosols and sulfur dioxide are markedly synergistic when reversible increases in airway resistance are used as the endpoint of response (Amdur and Underhill, 1968), but little has been done to determine if producation of chronic bronchitis or other chronic lung injury would result from prolonged exposures to the same combinations. Also as an example, Garner and McLean (1969) have shown that phenobarbital pretreatment potentiates the hepatotoxicity of a single dose of CCl_4, and it would be of value to know if the development of chronic liver cirrhosis would be enhanced with repeated low doses of CCl_4 given with chronic administration of phenobarbital.

> ***Recommendation 8–15:*** **The similarities or differences between acute and chronic injuries resulting from interactions of toxic agents should be evaluated.**

D. Interactions in Man

Stimulation of liver microsomal enzymes by slow release of organochlorine insecticides from fat storage sites, or by polynuclear hydrocarbons occurring as air pollutants or in cigarette smoke, may affect the doses of drugs required to maintain therapeutic blood levels (Conney, 1969). As an example, it seems that the relationships between various storage levels of organochlorine insecticides, or cigarette consumption, and the required therapeutic dosages of some drugs that are known to be metabolized by microsomal enzymes could be investigated in selected human population groups that are already under study for other purposes. There should be continuous exchange of information between biochemical toxicologists, clinical investigators and epidemiologists so that all groups will be alerted to the opportunities for collaborative or complementary research.

Recommendation 8–16: **Epidemiologic and experimental clinical investigations on interactions of toxic agents, based upon recent studies in animals, should be encouraged and supported.**

VII. Summary

Among the problems each Subtask Force and Subcommittee faced were problems of toxic effects, especially effects of low level prolonged exposures to mixtures of chemicals or to environmental toxic agents, in individuals sustaining multiple stresses of disease, of social pressures, and of heat, noise, or other physical factors.

Toxicology's role is an essential part of the complex control mechanism operating to ensure a wholesome environment. Toxicologists seek to detect evidence of impairment by noxious agents, to understand the basis for toxic injuries, and to recommend conditions of exposure that will not cause injury.

The Subcommittee on Toxicology recognized the overriding need for improvement in animal testing procedures to increase the usefulness of animal data in predicting human responses. Extensive programs to broaden the knowledge of responses in many species and strains are recommended with the specific purposes of relating these responses to those in man, "normal" or stressed.

A. Recommendations on choice of animal models

Toxicity studies should be conducted in an animal species that biotransforms the test substance in a manner similar to humans. If none of the readily available laboratory animals does so, a search for an animal model of the human pattern should be encouraged (Recommendations 8–2 and 8–4).

Use of "stressed" animals in studying effects of environmental pollutants offers an approximation of the exposures of stressed man. Many mammalian disease models are available; others should be developed, especially those relating to abnormal behavior patterns (Recommendations 8–12).

Toxicity data in several species should be compared with retrospective knowledge of human toxicity. Indications should emerge of the relative value of multiple species testing as compared with testing in one or two animal species (Recommendation 8–1).

In the absence of definitive data on the causes of variation of toxicity from species to species, and because animal strains of high reproducibility in response would make inter-laboratory comparisons much easier, highly inbred and random-bred strains of animals other than mice should be developed (Recommendation 8–3).

B. Recommendations concerning choice of tests for toxicity evaluation

1. Type of Test

"Early warning systems" (e.g., altered enzyme activities at doses of toxic agents far below those producing injury) if transposable to man, would permit safe studies in man and improved estimates of tolerated exposure levels. The use of behavioral or psychophysiologic tests in man exposed occupationally to noxious stimuli offers the possibility of detecting effects before any of the classical chemical or physical tests show changes (Recommendations 8-2 and 8-9).

2. Conditions and criteria.

a. Test Duration. The files of the FDA contain chronic toxicity reports probably unexcelled in extent. A staff toxicologist should review these studies to determine whether the qualitative or quantitative effects observed in tests lasting up to one year differ from those obtained in tests of longer duration (Recommendation 8–5).

b. Criteria

(1) Organ function: Analyses to detect aberrations in several of the steps in a sequence of reactions may reveal toxic displacements not seen in measuring only the overall product of the reaction chain. Automation of the procedures is essential to collect enough data under a variety of conditions so as to establish the validity of the new tests (Recommendation 8–6). Organ enlargement, when produced by exposure to a chemical or environmental constitutent, may be described as toxic if function tests reveal abnormalities (Recommendation 8–7). Morphologic changes (by light or electron microscope should be correlated with physiologic, biochemical, histochemical etc., observations to detect and assess toxic actions and mechanisms thereof. Routine electron microscopy should be discouraged in favor of EM studies of tissues known from other studies (histology, biochemistry) to be altered by the test substance (Recommendation 8–8).

(2) Biotransformation: Certain drugs and chemicals may drastically alter the activity of liver enzymes metabolizing foreign molecules, and thus change the effects of these foreign chemicals in the body. The prediction from animal studies of the effects of the combined exposures to toxic agents, drugs, etc., in man will require a knowledge of the similarity in species' response of biotransformation systems to factors altering foreign molecule metabolism. Only by systematic investigations of various species under various conditions can the nec-

essary background data be accumulated. Better estimates of the level of foreign compound metabolism in man are needed. Studies should be possible on readily available tissue (blood, urine), and estimates of metabolism by oxidative and non-oxidative pathways, and in liver and non-hepatic tissue should be sought (Recommendation 8–10).

(3) Interactions: A program for predicting adverse interactions of chemcals (drugs, environmental toxic agents) might be developed by computerizing pharmacologic, physiochemical, and exposure (dose, duration) data. Well-characterized interactions would furnish a basis for a pilot (validating) study (Recommendation 8–13).

Drug-metabolizing enzyme stimulation or inhibition helps to screen possible interactions (see section above). Multiple enzyme effects, competition for binding sites, storage sites, excretion, etc., should also be studied quantitatively and related to toxicity results in intact animals (Recommendations 8–11 and 8–14).

A systematic study of interactions causing acute or chronic injury should be done in such a way as to delineate similarities or differences in responses depending on duration of exposure and dose (Recommenduations 8–15 and 8–16).

BACKGROUND DOCUMENTS

Document Number	*Author*	*Title*
TX1–1	Murphy, S. D.	Interactions.
TX1–2	Golberg, L.	Function Tests and Morphological Assessment in Toxicology.
TX1–3	Hodge, H. C.	Duration of Toxicology Tests.
TX1–4	Hammond, P. B.	The Use of Animals in Toxicological Research.
TX1–5	Fouts, J. R.	Hepatic Microsomal Drug Metabolism and Its Relationships to Environmental Toxins, etc.
TX1–6	Mountain, J.	Notes on the Use of Stressed Animals in Toxicity Testing.

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PART IV

RECOMMENDATIONS ON SOCIAL AND BEHAVIORAL SCIENCES, TECHNOLOGICAL TRENDS, TRAINING AND ORGANIZATIONAL NEEDS

Chapter 9 Social and Behavioral Sciences

Chapter 10 Technological Trends

Chapter 11 Training

Chapter 12 Organization of Federally Sponsored Environmental Health Research

Chapter 9

SOCIAL AND BEHAVIORAL SCIENCES

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SOCIAL AND BEHAVIORAL SCIENCES*

I. Introduction

Men create most of their own environment. The cities, the buildings, the clothing, the food, the means of transportation and all of the other features of the world that people make or alter are a major part of the "natural environment" of modern man. In the process of creating these aspects of his environment, man has inadvertently created many of the most significant hazards to his health. These hazards arise not only out of the physical and chemical actions of environmental agents, but also out of social and psychological processes. Social and psychological processes help to create environmental hazards that contribute as much to morbidity and mortality as do many of the hazards that act through purely physical and chemical mechanisms. Furthermore, there are innumerable instances in which the technology is available for the prevention or elimination of environmental hazards, but it is not employed for personal, social or economic reasons.

The recommendations in this chapter are based upon two concepts of the relations between man and his environment which are fundamental to the understanding of the role of the environment in the production of human disease. The Subcommittee believes that these concepts should be stated explicitly.

First, for any organism the maintenance of life is dependent upon the acquisition and processing of information from the environment as well as upon the exchange of energy. For man, as for other higher animals, the central nervous system and the organs of special sense provide a major mechanism for the accomplishment of this function and for the elaboration of adaptive responses to the environment. Responses to information from the environment which are mediated by the human central nervous system may affect any bodily process which may be influenced either primarily or secondarily by the gross motor behavior of the person or by the action of any neural or endocrine effector system. Potentially such responses may have a major influence upon any disease process. They may determine the extent and nature of the exposure to any environmental agent which may cause disease; they may influence the reaction to any such agent; or they may, in themselves, lead to conditions that are regarded as "disease".

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*This chapter was prepared by a Subcommittee chaired by Dr. Lawrence E. Hinkle, Jr. and co-chaired by Dr. E. R. Crossman. Other people who participated in the preparation of this material included Drs. Alexander Cohen, Leonard B. Dworsky, Philip E. Enterline, and Demitri B. Shimkin.

Second, men live as members of social groups, and every man has complex relations to the people around him and to the groups of which he is a member. The requirements of their social roles and of their relations with other people make it necessary for men to make major adaptations, some of which may run counter to important biologic drives and homeostatic needs. These adaptations may significantly influence both behavior and physiologic processes. For these reasons the people with whom men relate and the social groups of which they are members are very important features of their environment. The processes by which the interaction between men and their environment create illness cannot be fully understood unless men are considered within the context of the social groups of which they are a part, and unless the various features of their illnesses and of their behavior are viewed as an outcome of the interaction of a number of factors, including the evaluation or perception of the information that men receive from their environment.

II. Social Variables as Determinants of the Distribution of Illness in the Population

In a complicated way the structure of human social groups contributes to the distribution of illness among their members and creates an unequal exposure to environmental health hazards. In the United States there are significant and rather strong positive associations between the amount of education a man has received, the type of occupation in which he is involved, the place where he lives, and the type of dwelling that he lives in. A large number of additional variables which are important to health are also involved in these associations. Among these are patterns of food intake, patterns of activity, and personal habits relative to dress, smoking and drinking. Within a society there are also many social groups based upon other shared characteristics such as ethnic background, religious affiliation, geographic area or occupation. The members of these groups also may share types of activity, preferences for various sorts of food or drink or exposure to other factors which may affect health.

The correlates of social structure act in many ways upon the distribution of illness. They often act together, and their effects may reinforce each other. As one moves downward through the social and economic categories in the United States, one finds an increase in the prevalence of a great many of the indicators of ill health (Kitagawa and Hauser, 1964; Pond, 1961; Public Health Service, 1962–1969). Abortion, still-birth and perinatal and infant mortality rates become higher; birth weights become lower; and congenital defects become more prevalent. Childhood illnesses and deaths become more frequent. Impairments of intelligence become more frequent, advancement in school is slower, sickness absence rates of school children are higher, and juvenile delinquency, school drop-outs and evidence of mental and emotional disturbances all become more frequent (Hatt and Reiss, 1957; Vedder, 1954). Rates for adult injury, sickness-absence and death become higher. Life expectancy becomes lower. Even disorders such as obesity, diabetes mellitus and coronary heart disease, which were once thought to be more prevalent among the well-to-do, now appear to be more prevalent in the lower economic and social groups, especially in urban areas (Stunkard, 1968, Public Health Service, 1962–1969—Series 10, No. 40, Series 11, No. 10). The relation between economic and social variables and health is not a simple one, and there are many exceptions to the general rule that there is an association between low-income and poor health. Also, there is good reason to believe that many of the phenomena that are statistically associated with income and education, for example, are primarily related to factors other than economics or education. Nevertheless, the overall evidence that social variables have a profound relation to health is impressive.

There is also a complex interrelation between social variables and physical features of the environment. Because of the association between income and housing, members of the lowest economic groups tend to live in the poorest housing in the least desirable areas of the community, in the central parts of the cities, adjacent to manufacturing areas, in lower lying lands, and along river bottoms. The problems associated with poor housing and crowding have been discussed in Chapter 4; the problems of differences in exposure to airborne pollutants have been mentioned in Chapter 1. As pointed out in Chapters 2 and 3, social determinants may similarly create differences in exposure to food-and-water-borne environmental hazards and to accidental traumata, and they create differences in the propensity of men to enter hazardous occupations and to live and work in places with a low level of sanitation. Even the genetic and "constitutional" determinants of disease may not be evenly distributed among social groups. There is a tendency for certain ethnic groups and groups of blood relatives to enter certain occupations or to live in certain areas. As a result, people who are systematically exposed to certain environmental or occupational hazards may be different from the remainder of the population in genetic characteristics that affect their susceptibility to disease as well as in their exposure to disease-producing environmental agents (Dunn, 1959; Goldschmidt, 1961).

The social variables that are associated with indicators of excess morbidity and mortality in the U.S. are associated with other social phenomena that are undoubtedly relevant to ill health and impaired development (Gordon, 1968; Abrams, 1965; Buell, *et al.*, 1952). In the lowest social and economic groups, mothers are likely to be less well educated, to marry earlier, and to have more children; they are more likely to become pregnant out-of-wedlock and to have children out-of-wedlock. They are more likely to be separated from the fathers of their children, and they are less likely to have a supporting male in the household. They are more likely to have to work in order to support their families and more likely to be partly supported by welfare payments. They are less likely to have adequate prenatal care and adequate attention at the time of delivery. Their lack of education, their low income, the frequent absence of a supporting male in the family, the presence of many other children, and the fact that the mother often has to work are factors which may lead to inadequate care for the children, inadequate nutrition, inadequate medical care, and impoverishment of the emotional and intellectual environment of the child.

All of these factors continue to operate in childhood. At this time also, in lower economic groups, many parents place less pressure upon their children to achieve in school. Social values of parents and of peer groups are such that they are more likely to be tolerant of poor performance in school and to be tolerant of forms of childhood and adolescent behavior which are classified by other groups as "juvenile delinquency". Smoking, drinking and the taking of drugs are more readily condoned and may even have a certain positive social value among the members of adolescent peer groups. Out-of-wedlock sexual activity by adolescent girls may have a similar positive value in certain peer groups. In adult life members of lower economic groups are more likely to enter hazardous occupations. They also receive less income and are less likely to receive adequate medical care.

Thus, there is an abundance of evidence that there is a close association between important social variables and important indicators of health. These associations have an effect such that the major health problems in the United States are to a large extent located in the same places as the major social problems: among the members of lower economic and social groups in urban and rural areas. The precise relation between the illnesses and the social problems is not clear, nor is it clear what intervention would be most effective in improving the health of those involved; but it is clear that the health problems of these people are in major degree an outgrowth of the environment in which they live, and that social and behavioral factors are probably the determining features of this environment.

The Subcommittee believes that the magnitude of the effects associated with social and economic variables is probably greater than that associated with any other single set of variables in the environmental area. It is also apparent that the aggregations of illness and disability within certain socially defined segments of the population, in rural as well as urban areas, constitute major health problems. It is urgent that some information be obtained in order to understand the mechanisms by which various elements of the social environment produce their adverse effects upon health and to understand what interventions should be undertaken in order to alleviate these effects.

> ***Recommendation 9–1:*** **It is recommended that population studies be undertaken with the purpose of defining better the mechanisms by which the social and economic aspects of the environment produce adverse effects upon health. These studies should be focused initially upon those segments of the population in which the greatest aggregations of illness, disability and social pathology appear to be present.**

In these studies special attention should be given to variables, such as congestion within households and in neighborhoods, patterns of interpersonal and intragroup relations, indicators of behavior, and interaction with various physical features of the environment (for example, distance to work or to play areas), as well as to variables such as education, income, housing, diet, infection, and availability of medical care.

While it is recognized that it will be important to focus upon some highly relevant indicators of health, such as infant mortality, child development, or juvenile and adolescent behavior, it will nevertheless be important to consider these in the context of total patterns of illness.

In the accomplishment of these investigations it is important that provision be made for the contribution and collaboration of people from any area of the biological, social, behavioral or environmental sciences which can contribute significantly to the understanding of the problem.

Finally, it appears that permanent population laboratories, taking the form of continuing institutions for the observation of population groups over periods of years, will be essential to the solution of many problems in these areas.

An important function of these laboratories will be to provide the resource base and organization to maintain continuing cumulative observations on a sufficient scale to gain decisive answers to many problems, to investigate social and behavioral phenomena of possible significance to health, and to estimate the probable relation of these to human behavior and performance and to indicators of morbidity and mortality. These population laboratories might also provide important inputs of data required to meet forecasting and intelligence responsibilities in the field of environmental health (see Chapter 10).

> ***Recommendation 9–2:*** **It is recommended that one or more permanent population laboratories be established. These should take the form of continuing institutions for the observation of populations over periods of years.**

III. Customs and Behavior as Determinants of Exposure to Environmental Hazards

At a simple and direct level, customs and behavior shared and sustained by the social group seem to be very important determinants of exposure to environmental hazards, and are sometimes a "hazard" in themselves.

The custom of smoking tobacco may be the single most important environmental health hazard in the United States at the present time (Public Health Service, 1967 and 1968). The habit has a pronounced social value for the individual, in that smoking a cigarette provides a socially acceptable mechanism for taking a brief respite from all sorts of tiring and demanding activities. The pharmacologic effects of smoking apparently provide transient relief from feelings of tension, anxiety, and fatigue. There is evidence that addiction to the habit occurs more readily in people who are especially subject to such symptoms.

The personal and social values that people receive from cigarette smoking have been so great, and the addictive power of the habit has been so strong, that most members of the smoking population have not been willing to give up the habit. Once it has been established, the withdrawal symptoms can be most unpleasant. The refusal of smokers to quit does not seem to be based upon ignorance of the harmful effects of smoking (Diehl, 1969). In fact, smokers appear to have an awareness of the harmful effects of smoking which is greater than that of non-smokers. They continue to smoke because of the gratification that they receive from smoking and because of the uncomfortable symptoms that they experience when they attempt to stop.

For apparently fortuitous reasons, alcohol and other intoxicating drugs have not been regarded as "environmental health hazards" even though they are recognized to be major health hazards. However, it is worthwhile noting that these, too, are agents whose consumption is based upon very ancient and widespread customs. The social and personal values provided by alcohol are recognized and institutionalized by our culture. Alcoholic drinks provide a socially acceptable means of producing transient feelings of well-being, of promoting human companionship, and of escaping transiently from some of the socially imposed restraints on behavior and speech. Their addicting qualities, the special susceptibility of certain members of the population for addiction and their secondary effects in producing accidents, illness and social disruption have been recognized since antiquity. Despite this, the social and personal values that are associated with drinking alcoholic beverages are such that no social mechanisms, whether economic, legal, or religious, have been effective in causing the population to give up the custom.

Customs related to food and modes of dress and adornment are also determinants of the prevalence of some kinds of disease. There are other customs of social groups which seem to play a role in the distribution of disease in a more subtle manner. There is evidence, for example, that obesity is more prevalent among the lower social and economic groups in the United States, especially in urban areas (Stunkard, 1968). This phenomenon seems to be, in part, related to the food preferences of people in these social categories, to the relative cheapness of the carbohydrate foods which they buy as compared to the relative expensiveness of the protein foods which they cannot afford, and possibly to the relative unawareness among such people of the consequences of consuming large amounts of carbohydrate foods. However, there is also reason to believe that a relative degree of obesity is regarded by many members of lower economic groups as evidence of robustness and good health and that well-fed and relatively obese people are more acceptable and attractive to them than are the relatively thin people who appear to be the upper and middle-class ideal.

Social customs and behavior appear to play a role in the distribution of accidental injuries and deaths. In American society the aggressive drives of young men are customarily channeled into socially acceptable sports, many of which are body-contact sports or team sports, and others of which, like skiing, involve some hazard. Such sports account for a good deal of the prevalence of the injuries in this age group. The aggressive drives, the social status and, to a certain extent, the courtship behavior of young men are also expressed by the possession of certain kinds of automobiles and motorcycles and by driving these rapidly and aggressively. Partly as a result of this, young unmarried males account for a disproportionate number of the automobile accidents that occur in the United States (McFarland and Moore, 1960; Markush, *et al.*, 1968). Another large proportion of automobile accidents can be attributed to the custom of drinking alcoholic beverages. If drinking and aggressive driving could be controlled, accidents, which are the largest cause of death for people in the second and third decade of life, might be reduced significantly.

It is important to consider the role of human behavior in determining the exposure of men to environmental health hazards which may cause disease. There is much evidence that people behave in a manner such that they expose themselves to environmental hazards and that this behavior may occur despite people's knowledge of the potential adverse affects that it may have upon their health. In each instance there is reason to believe that there are important combinations of physiologic, psychologic and social factors acting upon and within the individual which are involved in the production of this health-damaging behavior. There is also reason to believe that the understanding of the basis for this behavior and the development of alternative mechanisms for satisfying the needs of the persons which are involved in the behavior may be essential if the exposure of many people to potential environmental health hazards is to be prevented.

Recommendation 9–3: **Efforts should be made to initiate and support investigations to determine the basis for the various forms of human behavior which lead to voluntary exposure to potentially health-damaging agents and to develop methods of preventing such behavior or altering it so as to remove its health-damaging effects.**

IV. Social and Psychologic Factors as Determinants of the Effects of the Environment on Health

There are some features of the physical environment which are not in themselves hazardous to health, but which have adverse effects upon health because of the way that people perceive them and because of their effect upon the behavior of people, the relations between people, and the relation of people to their social groups.

In the United States there are few housing units which have features which clearly demonstrate an immediate and direct adverse effect upon health. Nevertheless, there is reason to believe that housing does contribute to ill health in several ways (see Chapter 4) through the effects of crowding, of disturbed interpersonal relations, disturbed behavior, disregard for cleanliness of person and the disposal of urine and feces, and deterioration of people's attitudes toward their worth and their opportunities for participation in the society, which lead to feelings of alienation from the social group as a whole.

Similar considerations apply to noise. Technically noise is "random sound" with no information content; but the popular definition of "noise" applies to any unwanted sound. Unwanted sound may have an adverse effect upon people, not because of its intensity or nature, but because it is unwanted. Noise, like housing, thus acquires its meaning as an adverse feature of the environment in part by virtue of social and psychologic determinants (see Chapter 4.)

The design and characteristics of major features of the environment such as cities, neighborhoods, and transportation units may acquire meaning as hazards to health by virtue of socially determined attitudes, values, and behavior. The configuration of an apartment building or a neighborhood may determine the forms of social interchange which take place among the people who live there. Networks of communication between family groups may be disrupted by some designs. The isolating effect of this upon women and old people, especially, may be severe. There may be an increase in morbidity, especially from disturbances of mood, thought, and behavior, as a result. The separation of mothers high in apartment buildings from children in play areas on the ground may lead to problems of mother-child relationships, and these in turn may lead to difficulties in maintaining bowel training in the very young and create conditions facilitating delinquent behavior in juveniles and adolescents.

Transportation facilities likewise have effects upon health. In large urban areas many people drive automobiles or ride in buses, trains, street cars, or subways for periods of an hour or more in commuting to and from work. Many of those who ride in public transportation spend all or part of the time standing up. There is reason to believe that transportation contributes significantly to the feelings of fatigue and tension that are a feature of life in urban society. The delays inherent in urban transportation systems, with their associated impacts on the lives of people who must meet time schedules, enhance these effects.

There is also evidence that the patterns of illness within a society are directly determined by the general patterns of life of those who live in the society (Dubos, 1965). A feature of life in modern urban societies is the prevalence of certain disturbances of mood, thought, and behavior, which seem to be directly related to chronic arousal and to sustained purposeful activity. In the general population, anxiety, feelings of tension, obsessive compulsive behavior, insomnia, and intermittent or chronic symptoms of asthenia, fatigue, depression, and agitation are exceedingly widespread. In addition to these manifestations, there are also widespread symptoms of muscle tension, of functional cardiovascular disturbances, of motor disturbances of the gastrointestinal tract, and of nasal vasomotor symptoms, among others, all of which appear to be related to the same processes which are involved in the production of the disturbances of mood, thought, and behavior which they often accompany.

In general, the hypothesis has been that the requirement for sustained purposeful activity and high levels of alertness during most of the daylight and early evening hours, sometimes continuing well into the night; the tight scheduling of human activities; the occurrence of contingent challenges; the changes in social forms and relationships; and the socialization of aggressive competition with concurrent restrictions on overt aggressive activities are among the features of these societies which have had much to do with the occurrence of the phenomena just described.

Although these phenomena may be important to the health of the population in general, they seem to have special relevance to the working environment. As pointed out in Chapter 3, there is an increasing number of occupations which require high levels of alertness and attention, long periods of sustained purposeful activity, and rapid decision making. The effective performance of people in these occupations may be crucial to the lives and welfare of many other people. For many industrial workers, the physiological and psychological effects of their activities, and the decrement in their function that may result when these are sustained, may have important health consequences.

Therefore, in the assessment of the potential health hazards represented by physical features of the environment, or by occupational activities, consideration must be given to the meaning of these to the people who are exposed to them and to their effects upon interpersonal and intergroup relationships and upon behavior. This is especially important in relation to the characteristics of occupations, of living and working spaces, of cities and means of transportation, and of problems presented by noise.

Recommendation 9–4: **Further research should be undertaken to determine the nature and degree of the physiological and psychological consequences and the ultimate effects upon health that are produced by men's perceptions of their environment, including the patterns of activity that these engender, their effects on interpersonal and group relationships, and their implications as determinants of human capabilities and of status and role within the society. It is also recommended that additional research be undertaken to determine how social processes generate and modify human perceptions of various aspects of the environment.**

V. Adverse Effects of the Environment on the Higher Functions of the Central Nervous System

Some of the most important adverse effects of the environment upon health may arise from effects upon the higher functions of the brain. As indicated in Chapter 8, a number of environmental agents, such as carbon monoxide, have their primary impact upon the highest neural functions. The subtle impairments that are the first indicators of their effects—disturbances of complex cognitive behavior, of decision-making, judgment, perception, and vigilance are difficult to distinguish from the effects of lack of sleep, fatigue, or physical illness, since they may involve similar mechanisms. Such impairments of brain function, whether transient or permanent, may lead to a serious deterioration of many important human activities, since they most seriously impair those faculties that are needed for creativity, responsibility, and the ability to adapt rapidly and appropriately to new and complex situations.

The Subcommittee believes that whenever the potential adverse effects of any agent in the environment are being considered, it is most important that the effects upon the higher functions of the central nervous system be fully evaluated. Too often the possibility of these effects is overlooked. Such effects should be sought, regardless of whether the aspect of the environment under consideration is a chemical agent that is inhaled or ingested, a physical agent such as heat or noise, or a job which requires sustained alertness and produces fatigue. Better instruments to measure these effects, and further research to define them more precisely, are needed.

***Recommendation 9–5:* Priority should be given to research to determine the effects of the environment on the highest functions of the central nervous system and for the development of the instruments needed for this purpose.**

VI. Conduct of Training

The conduct of needed research in the social and behavioral areas of environmental health and the effective exploitation of new models, instruments and techniques will make it necessary to have a carefully designed, continuing training effort. The National Institute of Mental Health's interdisciplinary training grants in neurobiology that have expedited the development of emerging fields like behavioral genetics and psychopharmacology, and the special fellowships that have permitted individuals trained in one discipline to receive support for training in another discipline, are useful models for the support of such training efforts.

Although the training of environmental health personnel is covered elsewhere in this report (Chapter 11), there is such a great need for the training of research specialists in combined areas and in emerging specialities of particular promise that it is again emphasized here. Examples of such areas include industrial behavior, behavioral toxicology, and human ecology. The number of such specialists need not be large, but the availability of resources and facilities to select and train an uninterrupted flow of "explorers of interfaces" of the highest possible quality must be vigorously stressed. Particularly important is sufficiently prolonged support for those selected so as to prevent interruptions and diversions from the individual's progressive development.

The Subcommittee has also pointed out the need for the behavioral science training of medical, bio-physical and other environmental health investigators. Here, apart from the development of a general understanding of the behavioral sciences, special attention should be given to (a) training in the nature and use of behavioral indicators of stress and illness; and (b) guided experience in field operations in target populations and communities and in industrial environments.

VII. Organizational Implications

The Subcommittee is of the opinion that the pervasive nature of social and behavioral phenomena in all interrelations between men and their environment calls for a corresponding recognition within the National Institute of Environmental Health Sciences. To meet this need, it is strongly urged that NIEHS organize a component for behavioral and social research (see Chapters 11 and 12). This component should include provision for an in-house capability to undertake important work such as the development of behavioral indicators of environmental insults, which might not be readily carried out on an extramural basis, and provision to plan and evaluate extramural work effectively.

VIII. Summary

The Subcommittee on Social and Behavioral Sciences has based its recommendations on two concepts which it believes to be fundamental: (a) that men's reactions to the people around them, and to the social groups of which they are members, may have a major influence on any disease process; and (b) that the effect of the environment on illness cannot be fully understood unless men are considered within the context of the social groups of which they are a part and unless their perceptions of their environment are considered also.

The Subcommittee recommended that population studies be undertaken to define better the mechanisms by which the social and behavioral aspects of the environment produce adverse effects upon health and to develop more effective methods of dealing with them. It has also suggsted that these be focused upon urban and rural groups in which there is a high concentration of problems of ill health, human development, and social pathology. In addition, it has been recommended that consideration be given to the establishment of population laboratories as an important mechanism for accomplishing this task (Recommendations 9–1 and 9–2).

The Subcommittee has recommended the initiation and support of investigations with the goal of determining the basis for the various forms of behavior which lead to exposure to potentially health damaging agents and with the goal of developing methods of preventing such behavior or of altering it so as to remove its health damaging effects. Particular examples are the behavior which leads to persistent cigarette smoking and the behavior which leads to the hazardous driving of automobiles by young men, both of which contribute significantly to important causes of death (Recommendation 9–3).

It is recommended that there be research to define further the effects that men's perception of their environment have upon health and the effects upon health that the environment itself produces through its influence upon the relations between people and social groups. It is also recommended that there be further research on the effects of the environment on the higher functions of the central nervous systems, which are reflected in sometimes subtle changes in mood, thought, and behavior, and that there be an effort to improve the instruments that are used to measure these (Recommendations 9–4 and 9–5).

Finally, it has been suggested that the Subcommittees on Training and Organization take cognizance of the important implications of the behavioral and social sciences for the education of investigators in the field of environmental health and that there be a permanent organizational component of the NIEHS with the capability of carrying out intramural research in the behavioral and social aspects of environmental health problems.

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Chapter 10

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TECHNOLOGICAL TRENDS*

I. Introduction

A. The Need for a National Forecasting Program

When originally organized, this Subcommittee hoped that it would be able to provide information to the separate Subtask Forces on the types of agents they should be concerned about in planning future research. It soon became clear that while some information necessary for such forecasts had been published, an organized environmental forecasting program had not been developed. There is, indeed, an urgent need for a forecasting program capable of timely and effective warning of technology-induced perturbations of any environmental factor which may have health implications.

Such forecasts can be made at a variety of levels. Examples can be cited ranging from (a) detailed and quantitative predictions of local concentrations of agents produced by established technologies, through (b) estimates concerning the nature of hazards associated with as yet undeveloped technologies, to (c) the assessment of the probability and environmental consequences of major accidents. Such predictions, both on a long and short range basis, are of interest. Each of these types of forecasts will have its place in predicting changes in environmental quality.

The need for environmental forecasting has grown with the pace of technological and community change. Forecasts of future technologies, based either on existing scientific knowledge or on as yet unknown concepts, are difficult but important to the environmental health field because of the speed with which new scientific concepts are converted into practice. This is well illustrated by the short time span between the development of the basic knowledge of nuclear fission and the successful operation of the first nuclear reactor. Similarly, there was a span of only a few years between the first suggestion of the possibility of microwave amplification of stimulated emission of radiation and the first operating unit.

The time period of diffusion of an invention is now estimated to be of the order of fourteen years, compared with thirty-seven years for technologies introduced early in this century (Schon, 1968). Examples of the rapid growth of new technologies include the use of microwave devices which have now become a $1.5 billion annual business, and of lasers, which are moving rapidly from laboratory and military use to commercial and possible home use. For example, it is estimated that 15,000 gas laser welding machines are already in commercial operation. A nearly fourfold increase in the annual consumption of titanium mill products is anticipated by 1978, and although figures on exact use and quantity are classified, a vastly increased use of beryllium parts has been reported in the ballistic missile program. Such rapid technological changes are potentially dangerous because the speed of the development may outstrip our ability to provide guidance and regulations for protecting environmental health.

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*This chapter was prepared by a Subcommittee chaired by Dr. Sheldon K. Friedlander. Other people who participated in the preparation of this material included Drs. Harrison Brown, George Bugliarello, Leonard B. Dworsky, Joseph J. Harrington, Theodore Hatch, and James Wei.

Future technologies offer greater latitude in preparing for the control of their impact on the health of the community than do established technologies. Timely warning of the onset of such technologies—in the form, for example, of "scenarios" portraying their possible effects on society—could better equip health officials to handle the resulting consequences. Thus, forecasts of new technologies should in some cases be performed even in the absence of scientific knowledge supportive of their feasibility. Even if the technologies fail to materialize—as can be expected in a large percentage of cases—a collection of continuously upgraded and revised "scenarios" could become a valuable tool for forecasting technology-induced environmental changes, for planning for their containment, or for suggesting alternative technologies.

B. *Methodology of Forecasting*

Attempts have been made in recent years to evolve a rational methodology for technological forecasting (Bright, 1968). Such methods can be classified into three groups:

1. *Intuitive Methods*

These include inspired guesses, "scenario" writings and techniques for reconciling the diverse opinions of many experts (e.g., the "Delphi" method).

2. *Extrapolations*

These include extrapolations of existing trends, ranging from those of a simple nature to those which take into consideration the emergence of other forces, as well as the possible depletion of certain resources. Also included in this category are envelope curves associated with a sequence of evolutionary developments.

3. *Correlation Methods*

These include cross correlations of the future trends of many events that have mutual-interactions such as the "Cross Impact Matrix" of Helmer and Gordon and the "Input-Output Matrix" of Leontief (Bright, 1968); systematic listings of all relevant factors and interactions such as the morphological box of Zwicky (Bright, 1968); normative forecasts, or consideration of the gap between what is needed and what is available; and mathematical modeling and simulation of complex systems where causes and effects are not obvious and could be much delayed in time.

While these methods are applicable to environmental forecasting, there is a need to develop a methodology specifically addressed to the environmental health field. One reason is that the identification of health-affecting agents likely to be produced in the future requires a higher order of sophistication than is provided by the usual technological forecasting. Adequate forecasting depends on the prediction of both the new technology and the environmental levels and health effects of its products and by-products. Moreover, technological-forecasting methodologies have not been integrated with demographic and behavioral forecasts defining the populations at risk and the intensities of expected exposures. In particular, predictions of such important variables as the daily and annual ranges of movement of individuals of varying ages, and in different socio-economic settings, will be needed.

Forecasting in the environmental health field will not be an isolated process. Reliable environmental forecasting methods can be expected, in their turn, to have a profound effect on technological trends. The selection of new technologies will, to a significant extent, be determined by their anticipated environmental impact. This is already the case in the automobile industry. The growth of new emission control technologies, such as the desulfurization of fossil fuels, will also be stimulated.

II. Examples of Forecasting in Environmental Health

Examples of forecasts in the environmental health field can be found in the published literature and obtained through discussions with experts in the field. Most forecasts are concerned with emission sources and levels and not with the problem of community exposure. The spectrum of such forecasts is so broad that it is useful to categorize them into groups according to the accuracy with which predictions can be made. In order of decreasing accuracy, these groups include:

A. Conventional Pollution

Emission levels of conventional pollutants can be predicted on a quantitative basis by estimating the changing rate of emission of the pollutant with existing emission controls (scrubbers, electrostatic precipitators, filters, etc.), by predicting the rate of development of the control technology and, finally, by taking into account the rate of diffusion of the control technology within the industry.

Assuming various control schedules, Rohrman, *et al.* (1965) have made studies of this type for sulfur dioxide through the year 2000; Fuller, *et al.* (1968) have made similar projections for hydrocarbons, oxides of nitrogen and carbon monoxide in Los Angeles through the year 1990. In the case of SO_2, projected annual emissions in the United States by the year 2000 were 76 million tons, approximately two to three times current levels. This figure is based on existing control technology. To estimate the effect of changing control technology on the range of future SO_2 emissions, Rohrman *et al.* (1965) selected two control schedules. The first, which they designated "severe but realistic", leads to a

SO_2 emission maximum of 41 million tons toward 1990, almost 50% above current emission levels. With the second control schedule, which they considered a maximum effort, SO_2 emissions were predicted to remain within the range of fluctuation of the last thirty years.

Similar studies of other agents such as lead, noise and pesticides would be of importance to planning in the environmental health field.

A major uncertainty in forecasting ambient pollution levels is the prediction of developments in control technology and instrumentation. This is an area of environmental forecasting in which some of the techniques that other researchers have developed for forecasting technological trends may prove particularly useful.

One type of forecasting model which has been applied to major sectors of the economy in a number of the metropolitan regions of the United States is the Leontief "input-output" model. For application to emission forecasts, this approach has the advantage over the independent extrapolation of emissions of specific pollutants in that an internally consistent projection is possible. Such consistency is achieved by accounting for the transfers of materials and other economic goods to and from each of the major economic sectors. Initial efforts in this field have been made by taking existing economic models (for Philadelphia and Boston) and extending them to include consideration of air, water, and solid pollutants. Although the successful application of such methods will require considerable improvements in the accuracy of the estimation of environmental emission factors, the ultimate benefits are well worth the added effort this will require.

B. New Products and Processes with Environmental Implications

This category has an extra dimension of uncertainty compared with pollution from conventional sources. Since the technology itself is only partially developed, the control technology and instrumentation are correspondingly more difficult to forecast. The result is that only qualitative predictions may be possible in certain cases. Examples of fields which bear scrutiny are new applications of metals, weather modification and innovations in pesticide research.

1. New Applications of Metals

According to a report of the National Academy of Engineering (NAS-NAE, 1969), beryllium is particularly attractive as a structural material in space and aircraft applications. This metal has a density almost as low, and a melting point much higher than magnesium. In addition, beryllium has a high thermal conductivity. For these reasons, it is of interest for structural purposes, and its use was considered for the disc brakes of the C–5A transport. The possible use of beryllium as a high-energy rocket fuel has been considered, but cost and toxicity have been drawbacks in this application.

Another metal for which new applications have been found is titanium. Ninety percent of its production is used in airframes, engines, and space hardware. This metal constituted about 0.2 to 0.3 percent of the airframe weight of commercial airliners put into service about ten years ago, such as the Boeing 707. Today the corresponding figure is 2 to 3 percent. More than 90 percent of the structural weight of the proposed supersonic transport would be titanium, utilizing between five hundred thousand and a million pounds of the metal per plane. There is also interest in the use of titanium tubing for heat-transfer in water desalination. If 10 percent of this market should go to titanium (copper-nickel is cheaper), 4 million pounds of titanium per year would be needed for this purpose by 1975. An almost four-fold increase in the annual consumption of titanium mill product is expected by 1978 (NAS-NAE, 1969).

Kahn and Wiener (1968, p. 79) have listed "one hundred areas in which technological innovation will almost certainly occur" by the year 2000 and, as one of their predictions, they suggest that inexpensive transuranium and other esoteric elements will be generally available. (The transuranium elements include neptunium, plutonium, americium, curium, berkelium, californium, einsteinium, fermium, and mendelevium with atomic numbers 93 through 101.) A thorough assessment of the potentialities of these developments appears almost mandatory if public health officials are to be able to plan for the control of future environmental health problems.

2. *Weather Modification*

In current techniques for weather modification, silver iodide is the substance most often used as a nucleating agent for rain stimulation, the suppression of hail and lightning, and the dissipation of supercooled fogs. Other substances reported to serve as nucleating agents are PbI_2, CuS, CuO, Cu_2O, BiI_2 (Byers, 1965). Organic materials also have been studied; Cadle (1966) mentions steroids, amino acids, phloroglucinol, alpha-phenazine, metaldehyde, trichlorobenzene, melamine and others.

In general, the quantities of materials used in weather modification experiments are small. They are dispersed within the environment, however, and, from the public health standpoint, there is a need to evaluate problems that might result from their biological concentration or local deposition in so-called "hot spots".

3. *New Pesticides*

It has been suggested that new pesticides will be developed in the enzyme and hormone categories, which will be more specific in their action on insects than current agents such as DDT. This is one example of a technological innovation which has the potentiality of counteracting an existing environmental hazard. Environmental health personnel, however, should be aware of the fact that such solutions may create new problems of their own.

C. Trace Element Analysis

There are a number of trace elements which are known to exist in the environment but which have not been shown to be harmful. Data resulting from improved instrumentation for the determination of such elements and from computerized multiple regression analyses may show that a correlation exists between certain trace organic compounds in drinking water and specific diseases such as stomach or intestinal cancer (McKee, 1969). Conversely, such data may show that the presence of one or more minerals, e.g., vanadium, copper and zinc, in low concentrations in drinking water is beneficial to human health, just as the intake of fluoride is now favored.

The ability to detect trace elements in the environment depends on advances in instrumentation as well as in methods of analysis. One technique which could prove useful in predicting such advances is trend curve analysis. For example, the limit of resolution in microscopy has been steadily reduced in past years with the evolution of the simple, the compound, the X-ray and, more recently, the electron microscope. Analysis of these improvements on a time base may help in predicting further developments in microscopy.

D. *Accident Probabilities*

What are the probabilities that a commercial nuclear power plant will have a serious accident resulting from a nuclear excursion, with the release of large amounts of radioactive material to the environment, or that during the transfer of biological or chemical warfare agents for disposal or storage, an air or rail accident will result in the release of significant quantities of the agent near an inhabited area?

Estimates of the probabilities of accidents involve compounding the probabilities of all events whose occurrence may lead to the hazard. The probabilities of certain events may be obtained from analyses of existing statistics—such as the probability of collision at a railroad crossing. On the other hand, the probability of other components of the total risk may be much more difficult to assess, because of a lack of information on a particular part of the total system, e.g., the probability of failure resulting from leakage of the welded joints on a stainless steel pressure vessel in a nuclear reactor, or the probability of human failure in the surveillance of the operation of the reactor. The ability to forecast accident probabilities is becoming an essential part of the overall evaluation of environmental health problems and research on this subject should receive increased attention in the future.

III. The Role of Formal Modeling Techniques in Forecasting

In the previous section, the emphasis has been on identifying and predicting emission levels of health-affecting agents produced by technology. In making detailed forecasts concerning community hazards, this information will have to be combined with models for predicting the transport, storage and reaction of pollutants in the environment and for assessing the resulting exposure of the community and its response. The past decade has seen the rapid development of mathematical models in these fields for use in forecasting and planning (Harrington, 1969). The integration of these submodels for the community-hazard system should be a major goal of the environmental health forecasting program.

There has been a rapid improvement in transport models such as those used for predicting water quality parameters, including dissolved oxygen in rivers and estuaries. The mathematical techniques principally involve systems of differential equations. Models for predicting, or simulating, the transport and dispersion of air pollutants are also becoming more comprehensive; examples include the range from urban areas to states and entire regions (Hilst, 1968). While the inputs to these models come from the forecasting of emissions, their output becomes the inputs for models of exposure of man. In this class are the mathematical models for predicting lead body burdens in man (Sterling, *et al.*, 1964).

Models for calculating the effects of a given pattern of exposure have also been developed. A recent example is the deterministic model of Friedlander (1968) for estimating the effect of an acute air pollution episode on a human population. Other models that belong to this category may be more epidemiologic in character, involving correlation and other statistical techniques.

Environmental health forecasting can play a significant role in inter-relating control programs in traditional problem areas such as air, water, solids and noise. This is important because of the increasing number of instances in which waste problems are shifted from one category to another as a result of process modifications or changes in control regulations. An example is the conversion of an air pollution problem into a potential water pollution problem by a gas scrubbing process. Another important use of inter-related models is in the development of monitoring and surveillance systems. Forecasting can never be considered wholly apart from such intelligence systems; formal forecasting models can help determine what data are needed, to what accuracy and precision they must be measured and where and how often they should be gathered.

Closely related to forecasting activities and monitoring and surveillance systems is the development of composite measures of environmental hazards and environmental health. Some examples are dissolved oxygen (DO) and biochemical oxygen demand (BOD) in water pollution control, indicator organisms (E. coli, for example) in water biology, and "oxidants" in air pollution programs. These measures represent a composite of more basic factors. They were devised with some regard for human health effects, the availability and cost of measuring techniques, the technology and economics of modifying the environment, and other organizational and socio-political factors. Composite measures, once established, are not particularly responsive to changes in the economy and technology, and the development of detailed models of the community-hazard system can provide a means for testing these indices.

Finally, a warning is in order: the development of comprehensive formal forecasting models will not be an easy task and such models will never eliminate the need for judgment. Their principal purpose is to reduce the burden on intuitive judgment by quantifying important consequences of alternative courses of action.

IV. Recommendations

Recommendation 10–1: **The Subcommittee on Technological Trends**

recommends that highest priority be given to the formation of a group with forecasting and intelligence responsibilities in the field of environmental health. Specifically, the group should have the following responsibilities:

1. To develop procedures capable of yielding at any time the best possible forecasts on sources, agents, community exposure and perturbation of community health.
2. To estimate the probabilities of accidents which might create serious environmental health problems.
3. To indicate areas where scientific, technological, economic, sociopolitical and behavioral research is needed to counter predicted environmental health threats and to suggest priorities for such research.
4. To indicate areas where research is needed to improve its own forecasting competence and to undertake, encourage and support such research.
5. To provide information to government agencies, industries and other groups which have operational responsibilities in the environmental health area.
6. To examine trends and to make forecasts on a global as well as on a national scale since environmental problems often transcend national boundaries.

Recommendation 10–2: In its operations, the forecasting and intelligence group should:

1. Treat the traditional environmental problem areas (for example, air, water, solid waste, noise) and their interfaces in a unified manner, taking into account shifts from one sector to another due to modification in technology and in control programs.
2. Establish close working relationships with other interested groups both within and outside the Department of Health, Education and Welfare. (The forecasting services should be particularly useful to the Environmental Quality Council.)
3. Coordinate its activities with those of similar groups which might be established in other countries and in international organizations.
4. Publish annually, in cooperation with other government agencies concerned, a forecast of technological hazards. Bulletins on new findings should be published to update the annual forecasts.
5. Conduct research intramurally and support it extramurally to take advantage of the skills present in industry, the university and other organizations.
6. Encourage the interdisciplinary training of personnel whose skills are critical to the forecasting process.
7. Foster communication of information by creating rotating "internships" from other groups within HEW and by establishing a broad program of visiting professionals from other groups both inside and outside the Federal Government.

V. Summary

There is an urgent need for a forecasting program capable of timely and effective warning of technology-induced perturbations of any given health parameter of the population. While certain aspects of the methodology of technological forecasting are applicable to environmental problems, there is a need to develop a methodology specifically addressed to the environmental health field.

Most existing environmental health forecasts are concerned with emission sources and levels and not with the problem of community exposure. Emission forecasts can be classified in order of the expected accuracy of prediction: (1) Quantitative forecasts have been made in the case of conventional pollutants such as sulfur dioxide and photochemical smog, but more such studies are needed. (2) Quantitative predictions of emission levels are more difficult in the case of new products and processes, such as new applications of beryllium and titanium or new pesticides. (3) Only rough estimates of contamination levels and effects are possible in the case of certain pollutants such as trace elements present in water. (4) Stochastic methods will be necessary in dealing with environmental effects produced by accidents.

The extension of long range estimations of emission levels and sources to projections of community hazards requires models for predicting the transport, storage and reaction of pollutants in the environment. The past decade has seen a rapid development of mathematical models in these fields. The Subcommittee believes that the integration of these submodels for the community-hazard system should be a major goal of environmental health forecasting programs.

The Subcommittee also pointed out that environmental health forecasting can play a significant role in inter-relating control programs in traditional problem areas such as air, water, solids and noise. This is important because waste problems may be shifted from one conventional category to another by process modifications or changes in control regulations.

Based on these considerations, the Subcommittee recommends that highest priority be given to the formation of a group with forecasting and intelligence responsibilities in the field of environmental health and that the group treat the traditional problem areas in a unified manner while coordinating its activities with those of similar groups both within and outside the Federal government as well as in other countries (Recommendations 10-1 and 10-2).

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TT-2	Wei, J.	Technological Forecasting Methods.
TT-3	Bugliarello, G.	Technological Forecasting for Environmental Health—Physical Factors and a Proposal for a Forecasting Mechanism.

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Chapter 11

TRAINING

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TRAINING*

I. Introduction

The report of the Task Force presents an extensive list of research needs in environmental health. To undertake any substantial portion of this research will require not only more resources, but above all a large number of highly trained and motivated scientists. Investigators must be recruited from those trained in fields ranging from the natural to the social and behavioral sciences. These people will, in turn, need to be equipped by special training or experience to address themselves to the complex problems of environmental health. Investigators trained to the doctorate level and beyond will be in urgent demand for research; it is also recognized that there will be a requirement for appropriate supporting sub-professional staff trained for research (Graber, 1968). Equally important, though not within the purview of this report, are those who must be trained for action programs.

Past and present programs encompass neither the number of individuals nor the scope of disciplines required in the future (Graber, 1968; Gross, 1962; Stevenson, 1969; NAS-NRC, 1962). Serious attention must also be given to the problem of attracting capable students in a variety of disciplines to the environmental health area. The essential need is to make such students aware of the fact that few fields today offer comparably stimulating and complex intellectual challenges combined with rewarding opportunities for service to mankind.

II. Essential Elements of Environmental Health Training

Environmental health science is not a unified discipline, but a diverse area of work with a rather specific mission. Research and training in this area, of necessity, draw heavily on the well-established disciplines. Certain of these disciplines relate to environmental health in a direct and obvious manner; others have more specialized application.

Training for research in environmental health science should be based upon sound graduate education in an academic discipline and rigorous preparation for original research. It should be characterized by an underlying concern for an orientation to the health of man.

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* This chapter was prepared by a Subcommittee chaired by Dr. Virgil H. Freed. Individuals who assisted in the preparation of the report were Drs. Hans L. Falk, James R. Fouts, Sheldon K. Friedlander, Paul B. Hammond, James D. Hardy, Ian T. T. Higgins, Lawrence E. Hinkle and Harold C. Hodge.

In the opinion of the Subcommittee, training programs in environmental health should exhibit several or all of the following elements. They should provide the trainee with:

1. An awareness of the broad spectrum of problems in environmental health;
2. An educational experience that includes (or builds upon) a strong disciplinary training in medicine, engineering, or science, and provides an understanding of, and an ability to deal with, complex, interrelated problems of environmental health;
3. Research training and experience on a problem which has a demonstrable relation to environmental health.

Where possible, the training program should be in a setting where a substantial program of research is ongoing and where there is a staff having a vital interest in teaching and graduate programs. Such an environment provides the trainee with the widest opportunity for exposure to a broad spectrum of environmental health research and environmental health problems. Such a setting also provides an opportunity for participation of staff in cooperative interdisciplinary activities. Under these conditions, the trainee is most likely to receive the programmed interaction and training needed for this field.

III. Disciplines of Importance to Environmental Health

No small group of disciplines alone can be considered fully qualified to deal with the breadth and complexity of these problems. Rather, the Subcommittee believes that the appropriate roles of many disciplines must be recognized. What follows, in the way of listing of disciplines, is intended to be illustrative rather than all-inclusive. It is recognized, of course, that since resources are in short supply, choices will have to be made in the training program. The criteria for judgment of relevancy offered above, in conjunction with an overall evaluation of program quality should, however, afford some help in making these choices.

A. Disciplines with Established Roles

The following are examples of disciplines whose role in environmental health has long been recognized and will continue to have a vital place in the field.

Biological Sciences—including microbiology, entomology, molecular biology, physiology, pathology, experimental psychology and some of the applied biological sciences.

Chemistry—including analytical, biochemical, organic, and physical chemistry.

Engineering—essentially all specialties but particularly environmental and sanitary engineering.

Medical Sciences—including such specialties as pharmacology and toxicology[*], epidemiology[**], nutrition, cancer (oncology), mutagenesis, teratology, occupational and environmental medicine, pathology, degenerative diseases, and gerontology.

B. Disciplines of Developing Importance

Other areas and disciplines are only now developing roles in environmental health. Some of these are described below, but no attempt has been made to indicate the various branches and specialties within them.

Environmental Biophysics—The generally accepted domain of health physics has been more or less limited to the study of the effects of electromagnetic radiation. However, the variety of physical factors in the environment extends well beyond this area to encompass heat, cold, humidity, sound and mechanical vibration. The environmental biophysicist of the future should be broadly trained in one or more of these fields (and he should be concerned particularly with the holistic response of the organism as well as the response at the molecular level). Further, certain aspects of meteorology might well be considered as a component of environmental biophysics.

Ecology—Ecological concepts are an invaluable component of the training of a variety of investigators in environmental health.

Mathematics and Statistics—Mathematics and statistics provide effective intellectual tools to deal with problems of great complexity. There is need for an increased number of trained statisticians oriented to health problems in environmental health sciences research; in addition, a number of mathematicians and bio-mathematicians should be encouraged to apply their talents to this field.

Operations Research or Systems Analysis—Closely related to mathematics and statistics is the field of operations research or systems analysis. This has developed as a defined body of knowledge, not only in mathematics but in engineering and other fields. These concepts are especially valuable in establishing relationships among elements of extremely complex problems and in organizing efforts leading to their solutions. For these reasons, it is important that systems analysts be encouraged to enter the field of environmental health research and that researchers already in this field be encouraged to include some training in systems analysis as part of their background.

Social and Behavioral Sciences[***]—Many if not most environmental health problems ultimately involve the human factor. This may take the form of a particular response or action of an individual on through the actions of society in general. At issue may be societal implementation of a particular practice that is required for abatement of an environmental health hazard. Or, it may be of a subtle interrelationship of the mind and emotions to the somatic health of the individual in response to environmental stresses.

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[*] Additonal comments on training needs in this field are given in Chapter 8.

[**] Additional comments on training needs in this field are given in Chapter 5.

[***] Additional comments on training needs in this field are given in Chapter 9.

Seldom is the natural scientist or engineer particularly well equipped by training to deal with such problems. It is felt essential that social and behavioral scientists be encouraged to enter this field.

IV. Motivation and Commitment of Trainees

Attracting students to environmental health sciences and motivating them demands high priority. The growth of enrollment in graduate programs related to environmental health indicates that success in this endeavor may not be too difficult (NAS-NRC, 1969). What has been lacking, heretofore, is a general knowledge of the opportunity and support available for training related to environmental health.

One very effective means of attracting and motivating the number of doctoral candidates that will be required in this field is the provision of adequate stipend and ancillary support. It matters little how much interest an individual may have in environmental health if financial resources are inadequate to allow him to pursue studies in this area. For this reason, serious consideration should be given both to the number of stipends available and the level of stipend support. It is unrealistic to establish a stipend level that fails to recognize rising costs of education as well as living. In a number of instances, the fixed boundaries of funds available for tuition has resulted in a reduction of the number of trainees as tuition costs rose. Future programs should be funded in such a manner that not only is there a periodic adjustment of the stipend level, but also flexibility to adjust to changes in tuition costs. The same arguments apply to the ancillary costs such as dependency allowances, and support for equipment and supplies.

Another means of attracting qualified students and securing a commitment to the environmental health field is to provide opportunity for undergraduates to work on summer projects. Such projects could take the form of specially designed programs, opportunities for research or summer work with agencies. In addition, special undergraduate research programs for participation during the academic year might be developed.

V. Defining and Meeting Research Training Needs

The explicit task of this section of the Task Force report has been to deal with research training needs in light of the research recommendations made in other sections. It is necessary, within the context of this assignment, to consider four questions, namely:

1. In what areas should research training be emphasized?
2. How many trained people will be needed in each area?
3. What new concepts, techniques and methods should be introduced into the training of one seeking to go into environmental research?
4. Are present methods of supporting training programs adequate and, if not, what are the alternatives?

It was concluded that to attempt to enumerate an all-inclusive list of disciplines relevant to environmental health would not be possible. Many disciplines are patently of importance in this area and portions of many others have or may have a germane relationship at a future time.

Current appraisals of manpower and forecasts of future needs in this area are far too imprecise to permit reliable estimates of research training needs. It is currently estimated that some 1,800 to 2,000 trainees are supported in various environmental health programs of which one-half to two-thirds are in programs leading to research careers (Graber, 1968; NAS-NRC, 1969). Such numbers are far too low to meet future needs, even if only a portion of the research recommendations of this report are to be implemented. A precise estimate of the number of individuals required in any given field is apt to fluctuate as problems change and new ones emerge. This means that training for research must be programmed on the basis of forecasts of research program needs.

There must be a substantial—probably several fold—increase in the support of training in order to ensure an adequate supply of professionally trained investigators. Current study indicates that in order to produce the required number of research workers in environmental health, training efforts will have to be approximately doubled in the next five years. University-based Environmental Health Science Centers should play a significant role in the total training effort. Encouragement and maintenance of such centers is important in this regard.

VI. Summary and Recommendations

A. Summary

On the basis of these and similar considerations, the Subcommittee has concluded that:

1. There is need for common concepts of, or criteria for, making judgments as to the relevancy of proposals for environmental health research and training programs. A key issue in the creation of such criteria is the *demonstrable importance* of the proposal to environmental health.
2. Environmental health research training should include two aspects: first, rigorous disciplinary study and, second, the provision of a broad conceptual framework with an extensive awareness of environmental health problems. The latter should include a component which provides integrative perspectives.
3. In addition to concern for training research workers, there is an essential requirement to train at a sophisticated level high caliber personnel representing a variety of disciplines for program planning and development, and for service as administrators and scientific specialists in a variety of programs.
4. Environmental health research provides intellectually exciting and challenging opportunities. These aspects, coupled with the intrinsic service to mankind permeating this field, would seem to provide the types of careers earnestly sought by many present day university students.

Programs should be established to make them aware of these opportunities.

5. A substantial portion of the burden for leadership and support of research training for environmental health rests with the National Institute for Environmental Health Sciences, since only an agency having a broad mission in environmental health can support the wide array of disciplines and innovations that must be brought to bear on these problems.

B. Recommendations

Evaluation of the foregoing findings and conclusions prompt the following recommendations.

Recommendation 11–1: **A vigorous program of expansion of support for training should be undertaken in a wide variety of disciplines relevant to environmental health.**

Recommendation 11–2: **A systematic, planned program of recruiting capable students in the area of environmental health research should be initiated. This program should include provision of seminars and courses at the undergraduate level to acquaint the student with and attract him to the field. Secondly, the program should include a stipend level realistically appropriate to the cost of living and ancillary support.**

Recommendation 11–3: **There should be developed and widely disseminated in the scientific community a statement of the qualitative criteria used for judging the environmental health relevance of graduate and post-doctoral training programs.**

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Chapter 12

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ORGANIZATION OF FEDERALLY SPONSORED ENVIRONMENTAL HEALTH RESEARCH*

I. Introduction

Early in its deliberations, the Program Committee explicitly recognized the necessity of the Task Force to concern itself with the organizational aspects of federal activities in environmental health. Particular attention was directed to those aspects related to the planning and vigor of the research programs in environmental health sciences. The Task Force was aware of certain problems associated with the series of reorganizations which have affected environmental health responsibilities within the Federal Government during the past several years, but considered it appropriate to deal with these only in the minimum detail essential for assessing the present research effort and its potential for development.

The Task Force which developed this report was initiated by the NIEHS to consider bio-medical research within the defined mission (Federal Register, 1969) of the Institute. As planning proceeded, however, it became evident that to do an effective job, the Task Force could not limit its concern solely to the mission of this Institute. As a result, many sections of the report deal with topics subject to other jurisdictions within the Federal Government. Where this occurs, it is hoped that the groups involved, such as the Consumer Protection and Environmental Health Services (CPEHS)** and the Federal Water Quality Administration (FWQA) will find the report helpful.

The present organizational pattern, wherein the control and regulatory agencies such as CPEHS and FWQA have responsibilities for the research directly related to their assigned control missions whereas the NIEHS must take a longer range approach aimed at a specification of the underlying health effects, appeared to the Task Force to be basically sound. These two efforts are complementary.

The public interest will be well served to maintain an activity which can in-

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* This chapter was prepared by a Subcommittee chaired by Dr. James L. Whittenberger. Individuals who contributed to its development included Dr. Delbert Barth, Mr. T. C. Byerly, and Drs. Leo Friedman, James D. Hardy, Paul B. Hammond, Morris A. Lipton, David Minard, Norton Nelson, Vaun A. Newill, Edward P. Radford, and Harold W. Wolf.

** Effective February 1, 1970, the Food and Drug Administration was separated from the Consumer Protection and Environmental Health Service and the name of the latter agency was changed to the Environmental Health Service.

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vestigate environmental health problems free of the inevitable competition between funds and staff needed for immediate regulatory purposes and those needed for desirable but "postponable" research not immediately relevant to such crisis problems. In addition, there is a normal human tendency to postpone undertakings which, however important, may uncover difficulties not now suspected and which may increase the difficulties of a regulatory agency already overburdened with responsibilities. This is not to say that agencies with regulatory responsibilities should not undertake longer range research endeavors nor that NIEHS should not assume some "firefighting" responsibilities. Both are desirable and appropriate; nevertheless, in the long range, the public health will be well served by the approach recognized in this organizational pattern.

This chapter is concerned mainly with the objectives of the key Federal agencies concerned with environmental health research, intramural-extramural relationships, mechanisms of extramural support, and associated administrative and legislative needs.

II. Objectives of NIEHS

What is now NIEHS was established at the National Institutes of Health with a primary goal to advance fundamental knowledge about the effects of environmental agents—chemical, physical, and biologic—upon the health of man. This mission includes the assignment to "(a) develop understanding of the mechanisms of action of such substances, (b) provide the scientific basis for evaluating their extent and severity on a national scale, and (c) diagnose, define and develop methods for treatment". Research is the principal and primary mission. Responsibilities for the control of environmental hazards, including the application of available knowledge of biological effects, were assigned to other agencies.

The mission of CPEHS (Federal Register, 1968) states in part that this agency "conducts and supports research to advance the knowledge of the impact of the environment upon man, and to identify those hazards having significant potential for harmful effects on the individual or his environment". For CPEHS research is one of many assigned tasks, and it is expected that most of its investigative programs will be targeted toward the identification and solution of environmental public health problems. The maintenance of free and effective communication between CPEHS and NIEHS is recommended to assure the complementary character of research efforts. This will be discussed in more detail below.

The primary goals of NIEHS, concerned as they are with the deleterious effects on health resulting from long term exposures to low-levels of environmental agents, alone and in combination, can be attained only by a coherent, imaginative, and uninterrupted program of research. While it is recognized that the Institute should be responsive to demands for work on immediate problems, these must be accepted on a selective basis. The special competence of the NIEHS laboratories will tend to attract such assignments and it is important that its primary programs not be damaged by frequent diversions of resources to these special tasks.

> ***Recommendation 12–1:*** **It is recommended that the Institute allocate a substantial portion of its resources to long-range studies and the development of efficient predictive techniques to aid in avoiding future health hazards. It is strongly urged that "ad hoc" assignments be kept in balance and that additional resources to support them be provided, if assignments require funds in excess of the Institute's usual budget.**

III. Intramural-Extramural Relationships

A sound Federal environmental health research program requires a broad array of considerations, ranging from the acquisition of the necessary physical space and special laboratory facilities to the deployment of Federal funds in scientific institutions outside the Government. With respect to the latter consideration, one of the most important aspects is that of intramural-extramural relationships.

An important element here is good communication, and efforts to this end will pay dividends to both parties. Specific suggestions are made later in this chapter on the possibility of joint sponsorship of several types of problem-oriented "centers". Easier exchange of personnel between Government laboratories and academic institutions would be of great value and would be enhanced by locating such laboratories on university campuses. This, too, is discussed in later sections of this chapter.

The use of external review groups on grant evaluation is an important form of communication, and curtailment of this type of involvement of the scientific community outside Government should be vigorously resisted. Agencies which do not use consultants on contract research would often benefit from greater use of outside advice, and this can be done without loss of the agency's decision-making responsibility.

The recent establishment of a "Center-directors" (see section V) group by NIEHS should be a major step in improving communication between NIEHS and the university-based environmental health centers. A further step which ought to be considered is whether CPEHS might develop a similar university-based group and whether the two groups should then have regular joint meetings on environmental problems of mutual interest.

The objective here is to build a direct and personal comprehension of environmental health problems in related agencies and in universities and to encourage through such contacts a basis for personal respect and collaboration.

IV. Mechanisms of Extramural Support

The mechanisms available to NIEHS for supporting non-profit institutions engaged in environmental health research are variable in scope and purpose. How the agency uses these mechanisms is an important determinant of the extent and success with which extramural research organizations and academic institutions can be involved in environmental health research and training.

The National Institutes of Health have traditionally maintained both intramural and extramural research programs. Intramural programs were designed to collect a "critical mass" of scientists from different disciplines within a limited geographical area like a building or a campus and to offer them adequate facilities and financial support with minimal teaching and administrative distractions so that they might achieve maximum research productivity in both basic and applied research related to specific disease categories. Extramural programs were designed to take advantage of the large amount and variety of talent on university campuses, their traditional teaching and training functions, and the flexibility and variety of their administrative and fiscal arrangements. The existence of both types of programs is also in accord with the general Federal approach of centralizing a core operation and decentralizing throughout the states whenever possible. Indirectly, extramural research programs offer major support to the maintenance and expansion of medical schools and other health-related institutions.

The ratio of intramural to extramural support varies considerably but has historically been about 1 to 8 in fully developed Institutes. The Gross Committee in 1962 (Gross, 1962) recommended the attainment of a ratio of 1 to 5 for Environmental Health Sciences by 1970. In view of the broad mission of NIEHS, together with the fact that a long range program is just now being developed, it is too early to specify what the optimum intramural to extramural ratio should ultimately be.

Recommendation 12–2: **It is recommended that the Director, NIEHS, be given maximum latitude in achieving an optimum balance between intramural and extramural support. A ratio of intramural:extramural of 1:5 is recommended and this should be accomplished as soon as possible, compatible with the orderly development of the intramural program. Reassessment of this ratio periodically should be, of course, encouraged.**

A. Contract Versus Grant Support

The Research Grant represents one of the basic mechanisms through which Federal agencies such as the NIEHS are able to support extramural research. Such support can also be provided through the mechanism of research contracts. Since contract expenditures are included in the intramural budget, however, the bulk of medical research in the areas of the categorical Institutes is in the form of research grants.

Since conceptual differences in these two mechanisms of research support are important, some of the usual characteristics of grants and contracts are listed below. These do not always apply, and under some circumstances the distinctions between these mechanisms are vague. Nevertheless, they are useful to discuss here.

1. Research Grants

Support relatively "basic" research
Long range objectives

Maximum freedom to investigator (within prescribed limits)
Available only to non-profit institutions
Flexibility in budgeting
"External" review by peer groups
Relative stability of funding
Less demand for "program relevance"
Assist in support of graduate training
Application initiated by investigator
Equipment purchased retained by institution at termination of the grant

2. *Research Contracts*

Delimited objectives with a known mode of approach
Action initiated and controlled by contracting agency
Research plans and progress subject to continuing review by project officer
Budget alterations relatively difficult to achieve
Initiation and termination more easily adjusted to budget fluctuations
Title to equipment retained by Government; equipment generally recalled after termination of the contract

Perhaps the most important distinctions are in the:

1. review mechanisms and
2. freedom of the investigator to exercise his scientific judgment

In regard to review mechanisms, the research grant application is handled by the anonymous peer judgment system which has been generally well regarded and which provides a mechanism for a high degree of quality control. Thus the philosophy and objectives of the two mechanisms are very different, although, as mentioned above, in specific examples it may be difficult to distinguish a grant from a contract. This blurring of the distinction involves the risk of losing the advantages usually credited to the two mechanisms for achieving the purposes they were designed to serve.

Recommendation 12–3: **It is recommended that the grant mechanism and the contract mechanism be used in accord with their distinct and different purposes. In general, the grant mechanism is most effective in enlarging the participation of academic institutions in environmental health research and research training.**

B. Program-Project Grants

A second and important research grant mechanism is the program project. This type of support is appropriate for a research program of established productivity and quality. The grant may provide core support as well as funds for an array of interrelated research projects having a central investigative focus. These grants are usually supported by a single agency but are sometimes supported by more than one.

C. Training Grants

A third type of grant available for the support of extramural research is the training grant. This type, of utmost importance to the graduate training function of academic institutions, is discussed in Chapter 11. The main factor which the Task Force would like to recommend at this point is that more consideration be given to having such grants at certain institutions be supported by several Federal agencies on a cooperative basis.

V. The Center Concept

Environmental health centers are proving an important source of strength in the national environmental health effort. Such centers can be developed both within and without the Federal establishment.

A. Extramural Centers

The concept of the university-based center grant program of NIEHS, although still in an evolutionary stage, provides for the support of a research and training activity in a university setting making optimal use of university and community resources. This represents a fourth grant mechanism for the support of extramural research.

The scope of such centers can vary from a relatively restricted field to quite diverse scientific interest. The interests, geographic distribution and pattern of operation of the present six university-based centers are well diversified.

The "center grant" mechanism is a sound approach to the development of stable centers of research and teaching which could not be readily secured by other mechanisms. The normal university organization and financing is not well adapted to the objectives sought here, namely a group of scientists and teachers of appropriate diversity and skills with career commitments to the several fields of environmental health. The presence of a "critical mass" of such full-time persons serves as a magnet to attract and interest the part-time collaboration of others in the university and in the community.

> ***Recommendation 12–4:*** **It is recommended that the number of such centers be increased in some degree, whether supported by NIEHS or other agencies. It is important to keep in mind, however, that center grant support cannot replace the extramural project grant support which can call on the complete body of scientific talent in universities and non-profit institutions.**

Some candidates for university-based centers are emerging which have interests extending well beyond the defined mission of NIEHS, although their program components are highly relevant to NIEHS. Additional programs should be developed which have major commitments to such fields as engineering control, nutrition, ecology, and mental health, to name a few.

In applying for Federal support, there is a normal tendency on the part of the staff of a potential center to shade the phrasing of the application in a manner to meet the stated mission of NIEHS, possibly leading to distortion of intention and probable restriction of scope. On the part of the supporting agency, a program which by its breadth extends into areas clearly beyond its responsibility constitutes an embarrassment and difficulty in defense before its own budget supporting unit. This dilemma could be resolved by a pattern under which major programs of considerable breadth, whether "center grants" or "program project" grants, were jointly financed on a continuing basis by two or more agencies having a clearly identified and substantiated interest in the program.

Recommendation 12–5: **It is recommended that means be devised for the joint evaluation and funding of major research-teaching programs, such as "center grants" and "program-project" grants jointly by several agencies where the program by its breadth covers in a major way the interests of these agencies.**

B. Intramural Centers

As in the case of university research programs, which have benefited by development of a few research "centers" with support for a core group of faculty members, a similar kind of development may be useful to intramural research programs within Federal agencies concerned with environmental health. The principle is that small groups of investigators may benefit by location in a specific geographic area, as for example, adjacent to special kinds of environmental problems or to unique resources.

Examples of such centers that have been established in other research areas include the Suicide Prevention Centers and the Center for Drug Abuse in Lexington. The concept deserves serious consideration by NIEHS and other Federal agencies in their efforts to develop improved research capability for dealing with specific environmental health problems.

Recommendation 12–6: **The Task Force recommends that specialized research centers be encouraged by those Federal agencies with responsibilities for environmental health research. Such centers would consist of groups of qualified investigators optimally located to study special problems.**

VI. Organization and Planning at the Federal Level

In the course of its discussions, the Task Force touched upon a number of other topics relative to the organization, planning and direction of environmental health research within the Federal Government.

Some commentary and a list of recommendations on these topics are given in the sections to follow.

A. Intramural Program Orientation

The Task Force made no attempt to study the internal organization of NIEHS, but noted a possible gap in the program which the Task Force believes should be remedied. This deficiency is described below and has been previously reviewed in more detail in Chapter 9.

An understanding of the effects of the environment on man cannot be achieved without an understanding of the interactions of man with that part of the total environment which is made up of other men and their complex social groups. The potential effects of environmental agents on man appear in many instances to be largely determined by behavioral and social factors.

It follows that a complete environmental health sciences research program must include an integrated segment devoted to the study of behavioral and social factors as they relate to environmental health. Such an organization should be capable of conducting a balanced intramural and extramural program in order to draw on the available scientific expertise in this field.

***Recommendation** 12–7:* **It is recommended that NIEHS develop communication links with scientists involved in behavioral and socal research and appoint staff to maintain communication at an appropriate organizational level. This component should provide an in-house capability to undertake special work such as the development of behavioral indicators of environmental insults and also to plan and evaluate extramural work effectively.**

B. Interagency Cooperation and Joint Program Planning

The field of environmental health is so broad in scope that no single existing Government agency has either the authority or the ability to solve all research problems. Thus, it is incumbent on all agencies with responsibilities in this field to coordinate fully their endeavors. The principal Government agencies involved are NIEHS and CPEHS in the Department of Health, Education and Welfare; the U.S. Atomic Energy Commission; and the Departments of Interior, Agriculture, HUD, Transportation, Commerce and Defense. Examples of possible cooperative endeavors relevant to problems described in the Task Force report are:

1. Greater cooperation in the gathering and exchange of information necessary for environmental health research. For example, it would be helpful if the National Center for Health Statistics developed and maintained a national death index for use in epidemiological investigations (see Chapter 5). Similarly, the records of the Social Security Administration might be made available to qualified epidemiologists.
2. Closer collaboration between Federal environmental health agencies and organizations such as the National Academy of Sciences (National Research Council), the National Science Foundation, and such professional groups as the Federation of American Societies for Experimental Biology, the American Institute of Biological Sciences, and the American Association for the Advancement of Science.
3. A planned program for exchange of research personnel among Federal agencies on a rotating basis. Not only could this assist in the training of such personnel, but it would also assure an understanding among younger personnel of the programs in each of the several agencies. Exchanges of this type were widely practiced during the 1950's between the Public Health Service and the U.S. Atomic Energy Commission.

Adequate coordination of research in environmental health by separate agencies is a necessary, but not a sufficient, condition for obtaining an optimum return for the dollars invested. The sufficient condition is possible only when all agencies coordinate their planning and evaluation of their ongoing research.

Recommendation 12–8: **It is recommended that there be established an explicit mechanism for the interchange of staff, both at the scientific and administrative levels, through specific assignments on joint projects and through an "exchange fellowship" arrangement between the Institute and related agencies. This could well be extended to similar arrangements between Government agencies and academic institutions.**

Recommendation 12–9: **It is recommended that NIEHS and CPEHS take the lead in developing a formal mechanism for joint planning and evaluation as well as coordination of environmental health sciences research projects of Government agencies.**

Another recommendation relates to more formal machinery for maintaining liaison between the several agencies. A liaison office has already been established within the Institute.

Recommendation 12–10: **It would be desirable to have parallel liaison offices established in the several Federal agencies having major environmental health responsibilities. It would, in addition, be desirable to establish a Federal Liaison Committee on the Environment which would include representatives from all such Federal agencies.**

It is recognized that there are other coordinating groups ranging up to the cabinet level Federal Council on Environmental Quality. These serve useful purposes, but what is proposed here is an organization at the "working level" to implement cooperative planning and execution of collaborative programs.

C. Location of Government Laboratories

In addition to interagency cooperation at the Federal level, there is a constant need to enhance, wherever possible, a close affiliation between Government research agencies and educational institutions. Such affiliations result in a number of mutual benefits. For the University, there is the availability of government employees with a wealth of practical experience and background at the operational level, who can participate in classroom, seminar, and laboratory teaching. Benefits to the government agency include an increased opportunity to hire persons who would otherwise be unavailable and who are of the quality desired to staff inhouse and contract research programs. Also of benefit is the opportunity to discuss agency programs with faculty colleagues and students.

When there is geographic proximity between the agency and the educational institution, other benefits are possible. There is the opportunity to work in the government laboratories on program-related projects, thereby increasing the output of the laboratory as well as increasing environmental health training. This work can range from participation at the technician level to the case in which a Ph.D. candidate completes his thesis research activity on a problem that would otherwise not be immediately explored. Another benefit to the government agency, moreover, is to have one or more university faculty members have part-time appointments to the government agency staff where they will spend part of their research time and utilize their talents performing agency program-related research.

Another factor which should be taken into consideration in locating new governmental laboratories is the nature of the research to be conducted in relation to geographical regions where the research projects will be directly applicable to problems of public concern. For example, if a new governmental laboratory were to be established to study the total effects of photochemical smog, an ideal location would be Los Angeles, California. Such a location would be virtually assured of public and political support.

***Recommendation 12–11:* It is recommended that, wherever possible, new government laboratories be located in close proximity to major universities and in a geographical region where the problem to be studied is of public concern. If, in a given situation, a site does not meet both these requirements, preference should be given to the site near a major university.**

D. Information Services and Exchanges

An important problem in all sciences today is that of keeping abreast of the flow of new information. Many agencies have been moving to meet this problem by establishing within their special areas abstracting and literature storage and retrieval capabilities. The functions of such activities are to provide for research and administrative personnel, both inside and outside the agency, up-to-date summaries of current knowledge in the field.

The Task Force believes that these activities within the NIEHS are appropriate and deserve continued support. Although related programs are being developed in chemical toxicology (in the National Library of Medicine), in air pollution (in the National Air Pollution Control Administration), and in pesticides, as well as in many other subject areas, the principle emerging in these developments is that specialized groups with their well-defined interests should be the basis of information in environmental health sciences. For maximum effectiveness, it is important that all such systems be compatible with each other and that their availability be made known among all the professions involved in environmental health research.

***Recommendation 12–12:* That information services in the NIEHS continue to be developed, with every effort being made to make storage and retrieval systems, so developed, compatible with other similar services relevant to environmental health.**

E. Legislative Needs

In the Task Force deliberations, only one area was identified in which legislation (or lack thereof) was a significant factor handicapping the conduct and growth of environmental health research. Although general legislative authority for occupational health research, training, and control activities in the Federal Government exists in the Public Health Service, this area of environmental health is not identified by special legislation and this has resulted in inadequate budgeting and has had a restrictive effect on development of leadership. This is regrettable, not only because of the illness and disability which could be avoided, but also because a strong occupational health unit could take advantage of the special opportunities to study health effects from specific pollutants in industrial exposures, gaining information that would be of value to all areas of environmental health. Properly directed, the additional research activities stimulated by appropriate legislation would provide the basic data needed for sound enforcement and control operations.

> ***Recommendation 12-13:*** **To meet urgent needs for defining and attaining national goals in occupational health, the Task Force recommends that support be given for appropriate legislation to strengthen and broaden federal programs in this field and to provide adequate authority to health agencies in the establishment of control methodology. The legislation should provide authority and funds for research on prevalence of industrial hazards, for health surveys of groups of workers, for development of criteria and standards for occupational exposures, for training, and for regulatory control.**

VII. Summary

The primary goal of the National Institute of Environmental Health Sciences is to advance fundamental knowledge about the biomedical effects of environmental agents. To assure the attainment of this goal, the Subcommittee recommends that the Institute allocate a substantial portion of its resources to long-range studies and the development of efficient predictive techniques to aid in avoiding future health hazards (Recommendation 12–1).

It is suggested that maximum utilization be made of the various mechanisms available for stimulation of environmental health research. In special cases, research contracts can serve as an effective mechanism for the support of extramural activities. In general, however, the grant mechanism (research and training grants and program project grants) is more effective for enlarging the participation of academic institutions in research and research training (Recommendation 12–3). Another grant mechanism of importance in making optimal use of university and community resources is the university-based center grant. Because this mechanism represents a sound approach for developing stable centers of research and teaching which cannot be readily secured by other means, it is recommended that the number of such centers be increased (Recommendation 12–4). Where the mission of such centers is broader than the mission of NIEHS, it is recommended that they be jointly supported by several agencies (Recommendation 12–5). It is also recommended that consideration be given to the establishment of such centers within NIEHS and other Federal agencies (Recommendation 12–6). To further promote close ties with universities, it is recommended that, wherever possible, new government laboratories be located in close proximity to major universities (Recommendation 12–11). As far as the program of NIEHS is concerned, an optimum ratio of 1:5 is suggested for intramural to extramural research (Recommendation 12–2).

Although the Task Force made no attempt to study the internal organization of NIEHS, one possible gap was noted which should be remedied. This was the need for an integrated segment devoted to the study of behavioral and social factors as they relate to environmental health. The addition of such a segment is recommended (Recommendation 12–7).

With respect to the coordination of environmental health programs at the Federal level, it is suggested that an explicit mechanism be established for the interchange of staff, both at the scientific and administrative levels, through specific assignments on joint projects and through an "exchange fellowship" arrangement between NIEHS and related agencies (Recommendation 12–8). It is also recommended that NIEHS take the lead in developing a formal mechanism for joint planning, evaluation, and coordination of environmental health sciences research projects at the Federal level. Some of this might be done through means of a Federal Liaison Committee, the establishment of which is suggested (Recommendations 12–9 and 12–10). As a final comment, it is recommended that NIEHS continue to develop information services, with every effort being made to make storage and retrieval systems, so developed, compatible with other similar services relevant to environmental health (Recommendation 12–12).

From the legislative standpoint, the Task Force believes that the area of greatest need is with respect to occupational health. The Task Force urges that support be given for appropriate legislation to strengthen and broaden Federal programs in this field (Recommendation 12–13).

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Federal Register (January 4, 1969). Vol. 34, No. 3, page 173.

Federal Register (December 20, 1968). Vol. 33, No. 247, page 19044.

Gross, P. M. (1962). Chairman, Report of the Committee on Environmental Health Problems. Prepared for the Surgeon General, Public Health Service, U.S. Department of Health, Education and Welfare. 288 pages. U.S. Government Printing Office, Washington, D.C.

APPENDICES

Appendix A	Organizational Structure of the Task Force
Appendix B	List of Background Documents
Appendix C	List of Attendees at Corvallis, Oregon, Meetings

APPENDIX A

ORGANIZATIONAL STRUCTURE OF THE TASK FORCE

Task Force on Research Planning in Environmental Health Science

Norton Nelson, Chairman
James L. Whittenberger, Co-Chairman

Hans L. Falk
James R. Fouts
Virgil H. Freed
Sheldon K. Friedlander
Leo Friedman
Paul B. Hammond
James D. Hardy
Ian T. T. Higgins
Lawrence E. Hinkle, Jr.

Harold C. Hodge
Paul Kotin
Brian MacMahon
Robert C. Mellors
David Minard
Edward P. Radford
Harold W. Wolf

NIEHS Staff
Samuel S. Herman
Samuel Price
Edward J. Lynch, Exec. Sec'y
Thomas M. Valega, Exec. Sec'y

Consultant—Bernard S. Pasternack

Substantive Research Areas

Subtask Force 1. Air Pollution	Subtask Force 2. Community and Industrial Exposures	Subtask Force 3. Food and Water Toxicology	Subtask Force 4. Physical Factors in the Environment
James L. Whittenberger, Chairman	David Minard, Chairman	Leo Friedman, Chairman	Edward P. Radford, Chairman
Ian T. T. Higgins, Co-Chairman	Harold C. Hodge, Co-Chairman	Harold W. Wolf, Co-Chairman	James D. Hardy, Co-Chairman
Morton Corn	Arend Bouhuys	John C. Ayres	George Bugliarello
Benjamin G. Ferris, Jr.	Edward R. Crossman	Leonard B. Dworsky	Alexander Cohen
Bernard G. Greenberg	Philip E. Enterline	Hans L. Falk	William T. Ham, Jr.
E. Cuyler Hammond	Theodore Hatch	Leon Golberg	Robert J. Hasterlik
Sheldon D. Murphy	Morris A. Lipton	Joseph J. Harrington	Demitri B. Shimkin
Jay A. Nadel	William H. Strain	Brian MacMahon	
William M. Thurlbeck		Herbert E. Stokinger	
James Wei		Gerald N. Wogan	

Areas of Common Interest to Subtask Forces

Subcommittee A: Epidemiology	Subcommittee B 1: Toxicology	Subcommittee B 2: Toxicology	Subcommittee C: Technological Trends	Subcommittee D: Social & Behavioral Sciences
Brian MacMahon, Chairman	James R. Fouts, Chairman	Hans L. Falk, Chairman	Sheldon K. Friedlander, Chairman	Lawrence E. Hinkle, Jr., Chairman
Ian T. T. Higgins, Co-Chairman	Leon Golberg	Leo Friedman	Harrison Brown	Edward R. Crossman, Co-Chairman
Arend Bouhuys	Paul B. Hammond	Leon Golberg	George Bugliarello	Alexander Cohen
Morton Corn	Harold C. Hodge	E. Cuyler Hammond	Leonard B. Dworsky	Leonard B. Dworsky
Philip E. Enterline	Morris A. Lipton	Edward P. Radford	Joseph J. Harrington	Philip E. Enterline
Benjamin G. Ferris, Jr.	Sheldon D. Murphy	James G. Wilson	Theodore Hatch	Demitri B. Shimkin
Bernard G. Greenberg	Herbert E. Stokinger	Gerald N. Wogan	James Wei	
Robert J. Hasterlik	William H. Strain			

APPENDIX B

LIST OF BACKGROUND DOCUMENTS*

Report Number	*Author*	*Title*
Subtask Force on Air Pollution		
AP–1	Higgins, I. T. T.	Epidemiological Studies of the Effect of Air Pollution.
AP–2	Murphy, S. D.	Use of Laboratory Animals to Assess the Effects of Air Pollution on Human Health.
AP–3	Corn, M.	Measurement of Human Exposure to Air Pollution in the Community.
AP–4A	Ferris, B. J.	Tests to Assess Effects of Air Pollutants on Human Health.
AP–4B	Nadel, J. A.	Technics for Measurement of Effects on Humans in Laboratory Experiments.
AP–4C	Greenberg, B. G.	Measurement of Effects upon Humans: Statistical and Epidemiological Aspects.
AP–5	Hammond, E. C.	A Hypothesis on Cancer Etiology and Pathogenesis.
Subtask Force on Community and Industrial Exposures		
CI–1	Hodge, H. C.	Health and Safety Hazards of Consumer Products.
CI–2	Hatch, T.	Concepts of Threshold Limits: Present Applications and Future Needs.
CI–3	Strain, W. H.	Prevalence, Hazards, and Mode of Action of Trace Elements.
CI–4	Bouhuys, A.	Respiratory Disease: Etiologic Role of Industrial Agents.
CI–5	Crossman, E. R. F.	Health Consequences of Industrial Environments on Perception, Decision-Making and Fatigue.
CI–6	Hatch, T.	Non-Specific Contributions of Environment to Ill Health.
CI–7	Smyth, H. F.	Some Research Needed on Systemically Toxic Atmospheric Contaminants in Industrial Exposures.
CI–8	Lee, D. H. K.	Notes on the Present Status of the Beryllium Problem.

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* These have been deposited with the National Library of Medicine. Copies may be secured on request to: National Library of Medicine, 8600 Rockville Pike, Bethesda, Maryland 20014.

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Subtask Force on Food and Water Toxicology

Report Number	*Author*	*Title*
FW–1	Wolf, H. W.	Microbiological Aspects of Potable Water.
FW–2	Stokinger, H. E.	Evaluation of the Toxic Potential of the Chemical Environment of Man—Water, Air, Food.
FW–3	Dworsky, L. B.	The Non-Food Uses of Water.
FW–4	Ayres, J. C.	Food Microbiology and Virology.
FW–5	Wogan, G. N.	Natural Toxicants and Contaminants in Food.
FW–6	Golberg, L.	Intentional Food Additives and Chemical Residues in Food.
FW–7:I	Freed, V. H.	Chemodynamics—Transport and Behavior of Chemicals in the Environment.
FW–7:II	Freed, V. H.	Toxicology of Pesticides.

Subtask Force on Physical Factors in the Environment

PF–1	Cohen, A.	Sound and Vibration.
PF–2:I	Ham, W. T. and Cleary, S. F.	Considerations in the Evaluation of the Biological Effects of Exposure to Microwave Radiation.
PF–2:II	Ham, W. T. and Clarke, A. M.	Lasers.
PF–3	Hardy, J. D.	Heat, Cold, Water Vapor and Infrared Radiation.
PF–4	Shimkin, D. B.	Space, Congestion, Crowding and Isolation: Preliminary Analysis of Problems and Potential Research.
PF–5	Hasterlik, R. J.	Ionizing Radiation.

Subcommittee on Epidemiology

EP–1	Hatch, T.	Non-Specific Contributions of Environment to Ill Health.

Subcommittee on Toxicology 1

TX1–1	Murphy, S. D.	Interactions.
TX1–2	Golberg, L.	Function Tests and Morphological Assessment in Toxicology.
TX1–3	Hodge, H. C.	Duration of Toxicology Tests.
TX1–4	Hammond, P. B.	The Use of Animals in Toxicological Research.
TX1–5	Fouts, J. R.	Hepatic Microsomal Drug Metabolism and Its Relationships to Environmental Toxins, etc.
TX1–6	Mountain, J.	Notes on the Use of Stressed Animals in Toxicity Testing.

Subcommittee on Toxicology 2

TX2–1:I	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part I.
TX2–1:II	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part II.
TX2–1:III	Falk, H. L.	Laboratory Assessment of Mutagenicity and Carcinogenicity. Part III.
TX2–1:IV	Falk, H. L.	A Review of Syn-, Co-, and Anti-carcinogenesis.
TX2–2	Wilson, J. G.	Environmental Hazards to the Reproductive Process.

Subcommittee on Technological Trends

Report Number	*Author*	*Title*
TT-1	Friedlander, S. K.	Forecasting Changes in Environmental Quality.
TT-2	Wei, J.	Technological Forecasting Methods.
TT-3	Bugliarello, G.	Technological Forecasting for Environmental Health—Physical Factors and a Proposal for a Forecasting Mechanism.

Subcommittee on Social and Behavioral Sciences

SB-1	Hinkle, L. E.	The Effects of the Social and Behavioral Aspects of the Environment on Human Health.

APPENDIX C

LIST OF ATTENDEES AT CORVALLIS, OREGON, MEETINGS

June 22 - July 12

1969

*Dr. John C. Ayres
Chairman, Food Science Division
University of Georgia
College of Agriculture
Athens, Georgia 30601

Dr. Delbert Barth
Director, Bureau of Criteria & Standards
National Air Pollution Control Administration
Environmental Health Service
411 West Chapel Hill Street
Durham, North Carolina 27701

Dr. Otto A. Bessey
Chief, Program Development & Evaluation Branch
National Institute of Environmental Health Sciences
National Institutes of Health
Westwood Building
Bethesda, Maryland 20014

Dr. Frank R. Blood
Director, Center for Toxicology
Vanderbilt University School of Medicine
Nashville, Tennessee 37203

Dr. Virgil C. Bokelheide
Head, Department of Chemistry
College of Liberal Arts
University of Oregon
Eugene, Oregon 97403

*Dr. Arend Bouhuys
Professor of Medicine & Epidemiology
Yale University School of Medicine
33 Cedar Street
New Haven, Connecticut 06519

---

* Members of the Task Force, its Subtask Forces, and its Subcommittees.

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*Dr. Harrison Brown
Professor of Geochemistry
Division of Geological Sciences
California Institute of Technology
Pasadena, California 91109

*Dr. George Bugliarello
Professor of Biotechnology & Civil Engrg.
Chairman Biotechnology Program
Carnegie Mellon University
Pittsburgh, Pennsylvania 15213

Mr. T. C. Byerly
Assistant Director
Science & Education
U. S. Department of Agriculture
Office of the Secretary
Administration Building, East Wing
14th & Jefferson Streets, S.W.
Washington, D.C. 20250

Dr. Edward M. Cohart
C.E.A. Winslow Professor of Public Health
Yale University School of Medicine
60 College Street
New Haven, Connecticut 06510

*Dr. Alexander Cohen
Bureau of Occupational Safety & Health
Environmental Health Service
U. S. Dept. of Health, Education & Welfare
1014 Broadway
Cincinnati, Ohio 45202

*Dr. Morton Corn
Professor of Occupational Health
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania 15213

*Dr. Edward R. Crossman
Professor of Industrial Engineering
Dept. of Industrial Engrg. & Operations Research
University of California
Berkeley, California 96720

Dr. Arthur B. DuBois
Professor of Physiology
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania 19104

*Mr. Leonard B. Dworsky
Director
Cornell University Water Resources & Marine Sciences Center
468 Hollister Hall
Ithaca, New York 14850

Dr. Robert Elder
Director, Division of Electronic Products
Bureau of Radiological Health
Environmental Health Service
U. S. Department of Health, Education, & Welfare
12720 Twinbrook Parkway
Rockville, Maryland 20852

*Dr. Philip E. Enterline
Professor of Biostatistics
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania 15213

*Dr. Hans L. Falk
Associate Director for Laboratory Research
National Institute of Environmental Health Sciences
National Environmental Health Sciences Center
P. O. Box 12233
Research Triangle Park, N.C. 27709

*Dr. Benjamin G. Ferris, Jr.
Associate Professor of Environmental Health & Safety
School of Public Health
Harvard University
665 Huntington Avenue
Boston, Massachusetts 02115

*Dr. James R. Fouts
Professor & Director of the Oakdale Toxicology Center
University of Iowa
Oakdale, Iowa 52319

•Dr. Virgil H. Freed
Director, Environmental Health Sciences Center
Oregon State University
Corvallis, Oregon 97331

•Dr. Sheldon K. Friedlander
Professor of Chemical Engineering & Environmental Health Engineering
Department of Environmental Engineering
California Institute of Tehnology
Pasadena, California 91109

•Dr. Leo Friedman, Director
Division of Toxicology
Bureau of Foods, Pesticides & Product Safety
Food & Drug Administration
U. S. Department of Health, Education, & Welfare
Washington, D. C. 20204

Mr. Richard Gallagher
Chief, Planning & Evaluation Branch
Office of Program Development
Environmental Health Service
U. S. Department of Health, Education, & Welfare
12720 Twinbrook Parkway, Room 510
Rockville, Maryland 20852

Dr. B. G. Giel
Public Health Service Liaison Officer
Bureau of Mines
U. S. Department of Interior
Washington, D. C. 20240

•Dr. Leon Golberg
Research Professor of Pathology
Albany Medical College of Union University
Institute of Experimental Pathology & Toxicology
Albany, New York 12208

•Dr. Bernard G. Greenberg
Professor of Biostatistics & Head
Department of Biostatistics
University of North Carolina
School of Public Health
Chapel Hill, North Carolina 27515

Mr. Charles N. Gregg
Office of the Assistant Secretary
for Health & Scientific Affairs
U. S. Department of Health, Education, & Welfare
HEW—North Building
Washington, D. C.

Dr. Clifford G. Grulee, Jr.
Dean, College of Medicine
Department of Environmental Health
University of Cincinnati
Eden Avenue
Cincinnati, Ohio 45219

Dr. A. J. Haagen-Smit
Division of Biology
California Institute of Technology
Pasadena, California 91109

*Dr. William T. Ham, Jr.
Professor of Biophysics & Head of Department
Department of Biophysics
Medical College of Virginia
Box 877
Richmond, Virginia 23219

*Dr. E. Cuyler Hammond
Vice President, Epidemiology & Statistics
American Cancer Society
219 E. 42nd Street
New York, New York 10017

*Dr. Paul B. Hammond
Professor, Department of Veterinary Physiology
& Pharmacology
College of Veterinary Medicine
University of Minnesota
St. Paul, Minnesota 55101

Mr. Gifford Hampshire
Acting Deputy Associate Director of Product Safety
Food & Drug Administration
U. S. Department of Health, Education, & Welfare
Crystal Plaza 5
2221 Jefferson Davis Highway
Arlington, Virginia 22202

•Dr. James D. Hardy
Professor of Epidemiology (Environmental Physiology)
Department of Epidemiology & Public Health
Yale University
290 Congress Avenue
New Haven, Connecticut 06519

•Dr. Joseph J. Harrington
Associate Professor of Environmental Health Engineering
School of Public Health
Harvard University
665 Huntington Avenue
Boston, Massachusetts 02115

•Dr. Robert J. Hasterlik
Professor of Medicine
Department of Medicine
University of Chicago
950 East 59th Street
Chicago Illinois 60637

•Dr. Theodore Hatch
Professor of Industrial Health Engineering, Emeritus
University of Pittsburgh
Fitzwilliam, New Hampshire 03447

Dr. Thomas A. Hayes
Medical Officer
Division of Surgical-Dental Drugs Surveillance
Food & Drug Administration
U. S. Department of Health, Education, & Welfare
2221 Jefferson Davis Highway
Crystal Plaza 5, MD-350
Arlington, Virginia 22202

Dr. Wayland J. Hayes, Jr.
Professor of Biochemistry
Division of Toxicology
School of Medicine, Station 17
Vanderbilt University
Nashville, Tennessee 37203

Mr. W. Ferguson Hawl
U. S. Department of Commerce
Environmental Sciences Services Administration
11800 Old Georgetown Road
Rockville, Maryland 20852

*Dr. Ian T. T. Higgins
Chronic Disease, Adult Health & Aging Unit
Department of Community Health Services
School of Public Health
University of Michigan
Ann Arbor, Michigan 48104

*Dr. Lawrence E. Hinkle, Jr.
Department of Medicine
New York Hospital—Cornell Medical Center
525 East 68th Street
New York, New York 10021

Dr. Warren G. Hoag
Professor & Director
Center for Laboratory Animal Resources
Michigan State University
East Lansing, Michigan 48823

*Dr. Harold C. Hodge
Chairman, Department of Phamacology
School of Medicine & Dentistry
University of Rochester
260 Crittenden Boulevard
Rochester, New York 14620

Dr. George B. Hutchison
Michael Reese Hospital & Medical Center
29th Street & Ellis Avenue
Chicago, Illinois 60616

Dr. Leon Jacobs
Assistant Director for Collaborative Research
National Institutes of Health
Building 1, Room 101
Bethesda, Maryland 20014

Mr. Thomas J. King
Deputy Director, Division of Planning Strategy
Environmental Health Service
U. S. Department of Health, Education, & Welfare
5600 Fishers Lane
Rockville, Maryland 20852

Mr. George W. Kingman
Executive Officer
National Institute of Environmental Health Sciences
National Environmental Health Sciences Center
P.O. Box 12233
Research Triangle Park, North Carolina 27709

*Dr. Paul Kotin
Director
National Institute of Environmental Health Sciences
National Environmental Health Sciences Center
P. O. Box 12233
Research Triangle Park, N.C. 27709

Dr. Herman F. Kraybill
Assistant Director for Biological Science Research
Bureau of Science
Food & Drug Administration
U. S. Department of Health, Education, & Welfare
FDA Building, Room 6816
200 C. Street, S.W.
Washington, D. C. 20204

Dr. Douglas H. K. Lee
Assoc. Director for Scientific Information
National Institute of Environmental Health Sciences
National Environmental Health Sciences Center
P. O. Box 12233
Research Triangle Park, North Carolina 27709

Dr. Marvin S. Legator
Chief, Cell Biology Branch
Division of Nutrition
Food & Drug Administration
U. S. Department of Health, Education, & Welfare
FDA Building, Room 1874
200 C. Street, S.W.
Washington, D.C. 20204

Mr. Eugene Lehr, Liaison Officer
Office of Environmental Impact
U. S. Department of Transportation
1002 Riddell Building
1730 K. Street
Washington, D.C. 20006

Dr. Joseph A. Lieberman
Assistant Administrator for Research & Development
Environmental Health Service
U. S. Department of Health, Education, & Welfare
5600 Fishers Lane
Rockville, Maryland 20852

*Dr. Morris A. Lipton
Department of Psychiatry, Medical School
University of North Carolina
Chapel Hill, N. C. 27515

Mr. Edward J. Lynch
Program Analyst
Program Development & Evaluation Branch
National Institute of Environmental Health Sciences
Westwood Building, Room 4A–10A
Bethesda, Maryland 20014

*Dr. Brian MacMahon, Head
Department of Epidemiology
Harvard University School of Public Health
665 Huntington Avenue
Boston, Massachusetts 02115

Dr. Rob S. McCutcheon
Scientific Administrator
Toxicology Study Section
National Institutes of Health
Room 226, Westwood Building
Bethesda, Maryland 20014

Dr. Robert Metzenberg
Department of Physiological Chemistry
University of Wisconsin School of Medicine
Madison, Wisconsin 53706

*Dr. David Minard
Professor & Chairman
Department of Occupational Health
The University of Pittsburgh
130 DeSoto Street
Pittsburgh, Pennsylvania 15213

Dr. Raymond T. Moore
Associate Commissioner
Environmental Health Service
U. S. Department of Health, Education, & Welfare
12720 Twinbrook Parkway, Room 303
Rockville, Maryland 20852

*Dr. Sheldon D. Murphy
Associate Professor of Toxicology
School of Public Health
Harvard University
665 Huntington Avenue
Boston, Massachusetts 02115

*Dr. Jay A. Nadel
Associate Professor
Department of Medicine
Cardiovascular Research Institute
University of California Medical Center
San Francisco, California 94122

*Dr. Norton Nelson
Director, Institute of Environmental Medicine
New York University Medical Center
550 First Avenue
New York, New York 10016

Dr. Vaun A. Newill
Director, Division of Health Effects Research
Bureau of Criteria & Standards
National Air Pollution Control Administration
U. S. Department of Health, Education, & Welfare
411 West Chapel Hill Street
Durham, North Carolina 27701

Dr. Bernard S. Pasternack
Associate Professor
Institute of Environmental Medicine
New York University Medical Center
550 First Avenue
New York, New York 10016

Dr. William W. Payne
Deputy Director
National Institute of Environmental Health Sciences
National Environmental Health Sciences Center
P. O. Box 12233
Research Triangle Park, North Carolina 27709

*Dr. Edward P. Radford
Professor, Department of Environmental Medicine
Johns Hopkins University
School of Hygiene & Public Health
615 N. Wolfe Street
Baltimore, Maryland 21205

Dr. Adam J. Rapalski
Division of Medical Sciences
National Research Council
2101 Constitution Avenue
Washington, D. C. 20418

Colonel John Redmond, Jr.
Preventive Medicine Division
Office of the Surgeon General
Department of the Army
Washington, D. C. 20315

Mr. Carlton C. Robinson
Automotive Safety Foundation
200 Ring Building
Washington, D. C. 20036

Dr. Robert T. Scholes
Assistant Associate Director for Extramural Programs
National Institutes of Allergy & Infectious Diseases
National Institutes of Health
Westwood Building, Room 703
Bethesda, Maryland 20014

Dr. Leslie Seyb
Director, Pacific Northwest Water Laboratory
Federal Water Quality Administration
200 S. W. 35th Street
Corvallis, Oregon 97330

•Dr. Dimitri B. Shimkin
Professor of Anthropology & Geography
University of Illinois
109 Davenport Hall
Urbana, Illinois 61801

Mr. Henry C. Steed
Director, Office of Grants Administration
Environmental Health Service
U. S. Department of Health, Education, & Welfare
12720 Twinbrook Parkway
Rockville, Maryland 20852

•Dr. Herbert E. Stokinger
Chief, Laboratory of Toxicology & Pathology
Bureau of Occupational Safety & Health
Environmental Health Service
U. S. Department of Health, Education, & Welfare
1014 Broadway
Cincinnati, Ohio 45202

*Dr. William H. Strain
Research Associate
Department of Radiology
School of Medicine & Dentistry
University of Rochester
260 Crittenden Boulevard
Rochester, New York 14620

Dr. H. Eldon Sutton
Professor of Zoology
Department of Zoology
The University of Texas
Austin, Texas 78712

*Dr. William M. Thurlbeck
Professor of Pathology
Department of Pathology
McGill University
3775 University Street
Montreal, Quebec, Canada

Dr. John R. Totter
Director, Division of Biology & Medicine
U. S. Atomic Energy Commission
Washington, D. C. 20545

Dr. Thomas Valega
National Institute of Environmental Health Sciences
National Institutes of Health
Westwood Building, Room 4A07
Bethesda, Maryland 20014

Dr. Niel Wald
Professor of Radiation Health
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania 15213

Dr. Charles F. Walters
Acting Executive Secretary
Air Pollution Research Grants Advisory Committee
National Air Pollution Control Administration
U. S. Department of Health, Education, & Welfare
801 North Randolph Street
Arlington, Virginia 22203

Mr. Ralph C. Wands
Director
Advisory Center on Toxicology
National Research Council
National Academy of Sciences
2101 Constitution Avenue
Washington, D. C. 20418

*Dr. James Wei
Senior Scientist
Mobil Research & Development Corp.
Central Research Division
P.O. Box 1025
Princeton, New Jersey 08540

Dr. Sidney Weinhouse
Director
Fels Research Institute
Temple University School of Medicine
Philadelphia, Pennsylvania 19140

*Dr. James G. Wilson
Department of Pediatrics & Anatomy
Children's Hospital Research Foundation
Elland Avenue & Bethesda
Cincinnati, Ohio 45229

Dr. Katherine S. Wilson
Executive Secretary
Genetics Study Section, RGRB
Division of Research Grants
National Institutes of Health
Westwood Building, Room 349
Bethesda, Maryland 20014

*Dr. James L. Whittenberger, Director
Kresge Center for Environmental Health
School of Public Health
Harvard University
665 Huntington Avenue
Boston, Massachusetts 02115

*Dr. Gerald N. Wogan
Associate Professor of Food Toxicology
Department of Nutrition & Food Sciences
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

*Dr. Harold W. Wolf
Chief, Division of Criteria & Standards
Bureau of Water Hygiene
Environmental Health Service
U. S. Department of Health, Education, & Welfare
12720 Twinbrook Parkway
Rockville, Maryland 20852

Dr. Arthur H. Wolff
Deputy Assistant Administrator for Research and Development
Environmental Health Service
U. S. Department of Health, Education, & Welfare
5600 Fishers Lane
Rockville, Maryland 20852

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